

Stahl's
Essential Psychopharmacology

Prescriber's Guide

ANTIDEPRESSANTS

SIXTH EDITION

Stephen M. Stahl



ROYAL GLAMORGAN HOSPITAL
Stahl's Essential Psychopharmacology

Prescriber's
Guide
Antidepressants

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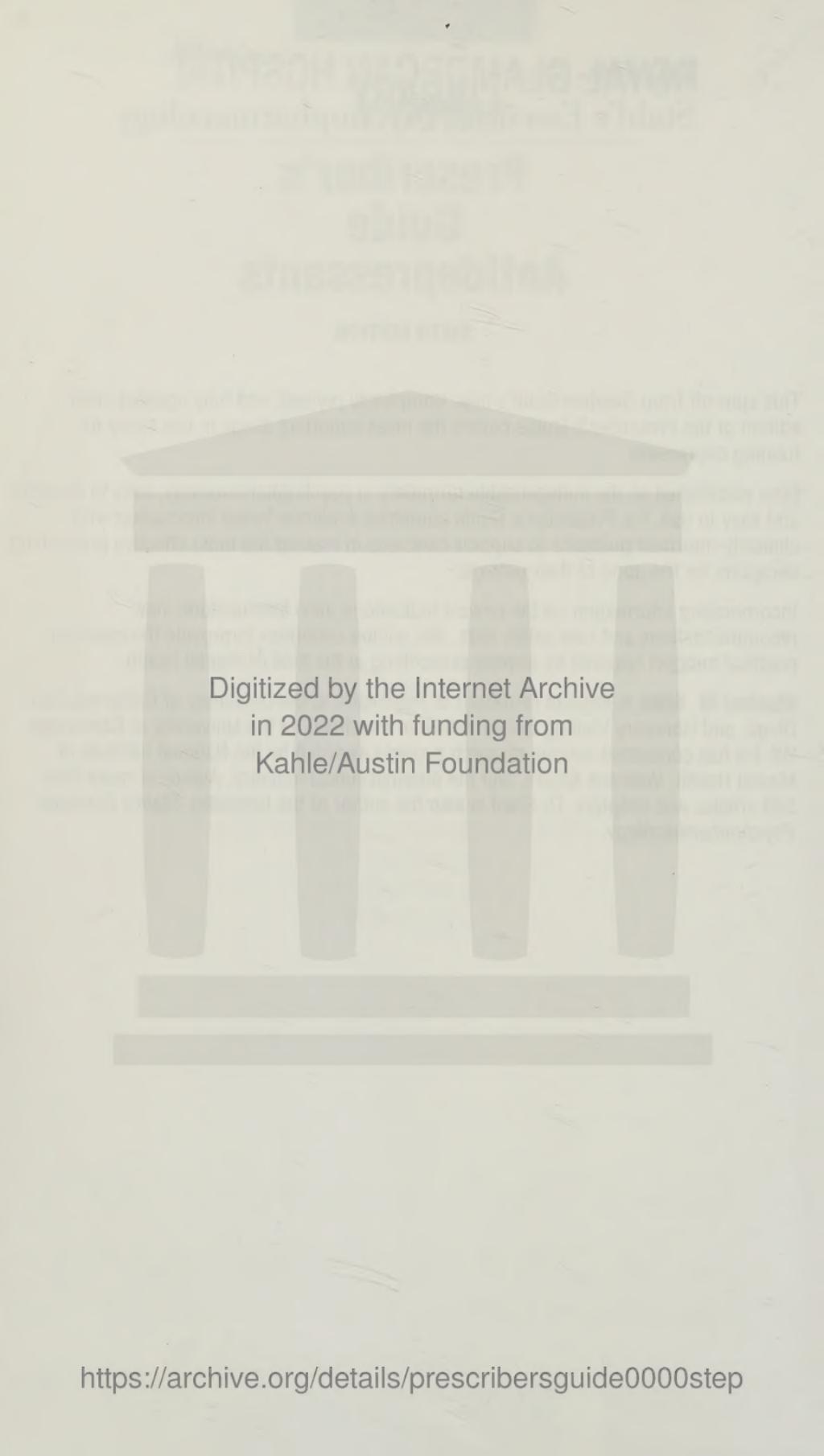
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Stahl's Essential Psychopharmacology

**Prescriber's
Guide
Antidepressants**

SIXTH EDITION

Stephen M. Stahl

University of California at San Diego,
San Diego, California

Editorial assistant
Meghan M. Grady

With illustrations by
Nancy Muntner



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Introduction

This *Guide* is intended to complement *Stahl's Essential Psychopharmacology*. *Stahl's Essential Psychopharmacology* emphasizes mechanisms of action and how psychotropic drugs work upon receptors and enzymes in the brain. This *Guide* gives practical information on how to use these drugs in clinical practice.

It would be impossible to include all available information about any drug in a single work, and no attempt is made here to be comprehensive. The purpose of this *Guide* is instead to integrate the art of clinical practice with the science of psychopharmacology. That means including only essential facts in order to keep things short. Unfortunately that also means excluding less critical facts as well as extraneous information, which may nevertheless be useful to the reader but would make the book too long and dilute the most important information. In deciding what to include and what to omit, the author has drawn upon common sense and 30 years of clinical experience with patients. He has also consulted with many experienced clinicians and analyzed the evidence from controlled clinical trials and regulatory filings with government agencies.

In order to meet the needs of the clinician and to facilitate future updates of this *Guide*, the opinions of readers are sincerely solicited. Feedback can be emailed to feedback@neiglobal.com. Specifically, are the best and most essential psychotropic drugs included here? Do you find any factual errors? Are there agreements or disagreements with any of the opinions expressed here? Are there suggestions for any additional tips or pearls for future editions? Any and all suggestions and comments are welcomed.

All of the selected drugs are presented in the same design format in order to facilitate rapid access to information. Specifically, each drug is broken down into five sections, each designated by a unique color background: ■ therapeutics, ■ side effects, ■ dosing and use, ■ special populations, and ■ the art of psychopharmacology, followed by key references.

Therapeutics covers the brand names in major countries; the class of drug; what it is commonly prescribed and approved for by the United States Food and Drug Administration (FDA); how the drug works; how long it takes to work; what to do if it works or if it doesn't work; the best augmenting combinations for partial response or treatment resistance; and the tests (if any) that are required.

Side effects explains how the drug causes side effects; gives a list of notable, life-threatening, or dangerous side effects; gives a specific rating for weight gain or sedation; and gives advice about how to handle side effects, including best augmenting agents for side effects.

Dosing and use gives the usual dosing range; dosage forms; how to dose and dosing tips; symptoms of overdose; long-term use; if habit forming, how to stop; pharmacokinetics; drug interactions; when not to use; and other warnings or precautions.

Special populations gives specific information about any possible renal, hepatic, and cardiac impairments, and any precautions to be taken for treating the elderly, children, adolescents, and pregnant and breast-feeding women.

The art of psychopharmacology gives the author's opinions on issues such as the potential advantages and disadvantages of any one drug, the primary target symptoms, and clinical pearls to get the best out of a drug.

In addition, drugs for which switching between medications can be complicated have a special section called The Art of Switching, which includes clinical pearls and graphical representations to help guide the switching process.

There is a list of icons used in this *Guide* following this Introduction and at the back of the *Guide* are several indices. The first is an index by drug name, giving both generic names (uncapitalized) and trade names (capitalized and followed by the generic name in parentheses). The second is an index of common uses for the generic drugs included in the *Guide* and is organized by disorder/symptom. Agents that are approved by the FDA for a particular use are shown in bold. In addition to these indices there is a list of abbreviations.

Readers are encouraged to consult standard references¹ and comprehensive psychiatry and pharmacology textbooks for more in-depth information. They are also reminded that the art of psychopharmacology section is the author's opinion.

It is strongly advised that readers familiarize themselves with the standard use of these drugs before attempting any of the more exotic uses discussed, such as unusual drug combinations and doses. Reading about both drugs before augmenting one with the other is also strongly recommended. Today's psychopharmacologist should also regularly track blood pressure, weight, and body mass index for most of his or her patients. The dutiful clinician will also check out the drug interactions of non-central nervous system (CNS) drugs with those that act in the CNS, including any prescribed by other clinicians.

Certain drugs may be for experts only and might include clozapine, thioridazine, pimozide, nefazodone, mesoridazine, and monoamine oxidase (MAO) inhibitors, among others. Off-label uses not approved by the FDA and inadequately studied doses or combinations of drugs may also be for the expert only, who can weigh risks and benefits in the presence of sometimes vague and conflicting evidence. Pregnant or nursing women, or people with two or more psychiatric illnesses, substance abuse, and/or a concomitant medical illness may be suitable patients for the expert only. Controlled substances also require expertise. Use your best judgment as to your level of expertise and realize that we are all learning in this rapidly advancing field. The practice of medicine is often not so much a science as it is an art. It is important to stay within the standards of medical care for the field, and also within your personal comfort zone, while trying to help extremely ill and often difficult patients with medicines that can sometimes transform their lives and relieve their suffering.

Finally, this book is intended to be genuinely helpful for practitioners of psychopharmacology by providing them with the mixture of facts and opinions selected by the author. Ultimately, prescribing choices are the reader's responsibility. Every effort has been made in preparing this book to provide accurate and up-to-date information in accord with accepted standards and practice at the time of publication. Nevertheless, the psychopharmacology field is evolving rapidly and the author and publisher make no warranties that the information contained herein is totally free from error, not least because clinical standards are constantly changing through research and regulation. Furthermore, the author and publisher disclaim any responsibility for the continued currency of this information and disclaim all liability for any and

¹ For example, *Physician's Desk Reference* and *Martindale: The Complete Drug Reference*.

all damages, including direct or consequential damages, resulting from the use of information contained in this book. Doctors recommending and patients using these drugs are strongly advised to pay careful attention to, and consult information provided by, the manufacturer.

List of icons



alcohol dependence treatment



alpha adrenergic blocker



alpha 2 agonist



anticonvulsant



antihistamine



antiparkinson/anticholinergic



benzodiazepine



beta blocker



cholinesterase inhibitor



conventional antipsychotic



dopamine stabilizer



lithium



medical food



l-methylfolate



modafinil (wake-promoter)



monoamine oxidase inhibitor



nefazodone (serotonin antagonist/reuptake inhibitor)



nicotinic partial agonist



N-methyl-D-aspartate antagonist



noradrenergic and specific serotonergic antidepressant



norepinephrine and dopamine reuptake inhibitor



sedative-hypnotic



selective norepinephrine reuptake inhibitor



selective serotonin reuptake inhibitor



serotonin-dopamine antagonist



serotonin and norepinephrine reuptake inhibitor



serotonin 1A partial agonist



serotonin partial agonist reuptake inhibitor



sodium oxybate



stimulant



thyroid hormone



trazodone (serotonin antagonist/reuptake inhibitor)



tricyclic/tetracyclic antidepressant



vortioxetine



How the drug works, mechanism of action



Best augmenting agents to add for partial response or treatment resistance



Life-threatening or dangerous side effects



Weight Gain: Degrees of weight gain associated with the drug, with unusual signifying that weight gain has been reported but is not expected; not unusual signifying that weight gain occurs in a significant minority; common signifying that many experience weight gain and/or it can be significant in amount; and problematic signifying that weight gain occurs frequently, can be significant in amount, and may be a health problem in some patients



Sedation: Degrees of sedation associated with the drug, with unusual signifying that sedation has been reported but is not expected; not unusual signifying that sedation occurs in a significant minority; common signifying that many experience sedation and/or it can be significant in amount; and problematic signifying that sedation occurs frequently, can be significant in amount, and may be a health problem in some patients



Tips for dosing based on the clinical expertise of the author



Drug interactions that may occur



Warnings and precautions regarding use of the drug



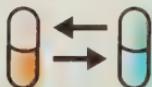
Dosing and other information specific to children and adolescents



Information regarding use of the drug during pregnancy



Clinical pearls of information based on the clinical expertise of the author



The art of switching



Suggested reading

THERAPEUTICS

Brands • Valdoxan*see index for additional brand names***Generic?** No**Class**

- Neuroscience-based Nomenclature: melatonin multi-modal (Mel-MM)
- Agonist at melatonergic 1 and melatonergic 2 receptors
- Antagonist at 5HT2C receptors

Commonly Prescribed for*(bold for FDA approved)*

- Depression

**How the Drug Works**

- Actions at both melatonergic and 5HT2C receptors may be synergistic and increase norepinephrine and dopamine neurotransmission in the prefrontal cortex; may resynchronize circadian rhythms that are disturbed in depression
- No influence on extracellular levels of serotonin

How Long Until It Works

- Daytime functioning, anhedonia, and sleep can improve from the first week of treatment
- Onset of full therapeutic actions in depression is usually not immediate, but often delayed 2–4 weeks
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine is stopped
- Continue treatment until all symptoms are gone (remission)
- Once symptoms gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose as early as 2 weeks after initiating treatment if response is insufficient (decision on dose increase has to be balanced with a higher risk of transaminase elevation; any dose increase should be made on an individual patient benefit/risk basis and with strict respect of liver function tests monitoring)
- Consider switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer

**Best Augmenting Combos for Partial Response or Treatment Resistance**

- SSRIs (excluding fluvoxamine), SNRIs, bupropion, reboxetine, atomoxetine (use combinations of antidepressant with caution as this may activate bipolar disorder and suicidal ideation)
- Modafinil, especially for fatigue, sleepiness, and lack of concentration
- Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression, or treatment-resistant depression
- Benzodiazepines

Tests

- Liver function tests before initiation of treatment and then after around 3 weeks, 6 weeks, 12 weeks, 24 weeks, and thereafter when clinically indicated
- When increasing the dose, liver function tests should be performed at the same frequency as when initiating treatment
- Liver function tests should be repeated within 48 hours in any patient who develops raised transaminases

SIDE EFFECTS

How Drug Causes Side Effects

- Adverse reactions usually mild to moderate and occur within the first 2 weeks of treatment
- Actions at melatonergic receptors and at 5HT2C receptors could contribute to the side effects described below

Notable Side Effects

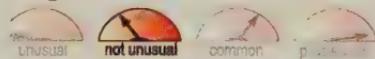
- Nausea and dizziness are most common
- Other adverse reactions are somnolence, fatigue, insomnia, headache, anxiety, diarrhea, constipation, upper abdominal pain, vomiting, hyperhidrosis
- Increase of transaminase levels



Life-Threatening or Dangerous Side Effects

- Rare hepatitis, hepatic failure
- Theoretically rare induction of mania (class warning)
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24) (class warning)

Weight Gain



- Occurs in significant minority
- Cases of weight decrease have been reported

Sedation (Somnolence)



- Occurs in significant minority
- Generally transient
- May be more likely to cause fatigue than sedation

What to Do About Side Effects

- Wait
- Wait
- Stop if transaminase levels exceed 3 times the upper limit of normal
- Switch to another drug

Best Augmenting Agents for Side Effects

- Often best to try another antidepressant monotherapy prior to resorting to

augmentation strategies to treat side effects

- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Many side effects cannot be improved with an augmenting agent
- Therapeutic activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of agomelatine (class warning)

DOSING AND USE

Usual Dosage Range

- 25–50 mg/day at bedtime

Dosage Forms

- Tablet 25 mg

How to Dose

- Initial 25 mg/day at bedtime; after 2 weeks can increase to 50 mg/day at bedtime



Dosing Tips

- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar disorder and switch to a mood stabilizer or an atypical antipsychotic

Overdose

- Drowsiness and epigastralgia; fatigue, agitation, anxiety, tension, dizziness, cyanosis, or malaise have also been reported

Long-Term Use

- Treatment up to 12 months has been found to decrease rate of relapse

Habit Forming

- No

How to Stop

- No need to taper dose

Pharmacokinetics

- Half-life 1–2 hours
- Metabolized primarily by CYP450 1A2



Drug Interactions

- Use of agomelatine with potent CYP450 1A2 inhibitors (e.g., fluvoxamine) is contraindicated
- Tramadol increases the risk of seizures in patients taking an antidepressant (class warning)



Other Warnings/ Precautions

- Use with caution in patients with hepatic injury risk factors, such as obesity/overweight/non-alcoholic fatty liver disease, diabetes, patients who drink large quantities of alcohol and/or have alcohol use disorder, or who take medication associated with risk of hepatic injury. Doctors should ask their patients if they have ever had liver problems.
- If symptoms or signs of potential liver injury (dark urine, light-colored stools, yellow skin/eyes, pain in upper right belly, sustained new-onset and unexplained fatigue) are present, agomelatine should be discontinued immediately
- Use caution in patients with pre-treatment elevated transaminases (> the upper limit of the normal range and ≤ 3 times the upper limit of the normal range)
- Discontinue treatment if serum transaminases exceed 3 times the upper limit of normal; liver function tests should be performed regularly until serum transaminases return to normal
- Agomelatine should be administered at bedtime
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- When treating children off label (an unapproved use), carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately

- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient has hepatic impairment
- If patient has transaminase levels > 3 times the upper limit of normal
- If patient is taking a potent CYP450 1A2 inhibitor (e.g., fluvoxamine, ciprofloxacin)
- If patient is taking an MAO inhibitor (MAOI)
- If patient has galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption
- If there is a proven allergy to agomelatine

SPECIAL POPULATIONS

Renal Impairment

- Drug should be used with caution

Hepatic Impairment

- Contraindicated

Cardiac Impairment

- Dose adjustment not necessary

Elderly

- Efficacy and safety have been established (< 75 years old)
- Dose adjustment not necessary
- Should not be used in patients age 75 years and older
- Should not be used in elderly patients with dementia



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Safety and efficacy have not been established and it is not recommended



Pregnancy

- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester

AGOMELATINE (continued)

- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy

Breast Feeding

- Unknown if agomelatine is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- Therefore, breast feeding or drug needs to be discontinued
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients with lack of energy, anhedonia, anxious comorbidity, and sleep-wake disturbances
- Patients particularly concerned about sexual side effects

Potential Disadvantages

- Patients with hepatic impairment

Primary Target Symptoms

- Depressed mood, anhedonia
- Functioning
- Anxiety within depression



Pearls

- Agomelatine represents a novel approach to depression through a novel pharmacologic profile, agonist at melatonergic MT1 / MT2 receptors and antagonist at 5HT2C receptors acting synergistically
- This synergy provides agomelatine with a distinctive efficacy profile, different from conventional antidepressants with potentially an early and continuous improvement over time
- Agomelatine improves anhedonia early in treatment
- Improves anxiety in major depressive disorder
- May be fewer withdrawals/discontinuations for adverse events than with other antidepressants
- No significant effect on cardiac parameters such as blood pressure and heart rate
- Some data suggest that agomelatine may be specially efficacious in achieving functional remission
- Agomelatine may improve sleep quality by promoting proper maintenance of circadian rhythms underlying a normal sleep-wake cycle



Suggested Reading

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THERAPEUTICS

Brands • Solian

see index for additional brand names

Generic? No**Class**

- Neuroscience-based Nomenclature: dopamine receptor antagonist (D-RAn)
- Atypical antipsychotic (benzamide; possibly a dopamine stabilizer and dopamine partial agonist)

Commonly Prescribed for

(bold for FDA approved)

- Schizophrenia, acute and chronic (outside of USA, especially Europe)
- Dysthymia

**How the Drug Works**

- Theoretically blocks presynaptic dopamine 2 receptors at low doses
- Theoretically blocks postsynaptic dopamine 2 receptors at higher doses
- May be a partial agonist at dopamine 2 receptors, which would theoretically reduce dopamine output when dopamine concentrations are high and increase dopamine output when dopamine concentrations are low
- Blocks dopamine 3 receptors, which may contribute to its clinical actions
- Unlike other atypical antipsychotics, amisulpride does not have potent actions at serotonin 2A or serotonin 1A receptors
- Does have antagonist actions at serotonin 7 receptors and serotonin 2B receptors, which may contribute to antidepressant effects

How Long Until It Works

- Psychotic symptoms can improve within 1 week, but it may take several weeks for full effect on behavior as well as on cognition and affective stabilization
- Classically recommended to wait at least 4–6 weeks to determine efficacy of drug, but in practice some patients require up to 16–20 weeks to show a good response, especially on cognitive symptoms

If It Works

- Most often reduces positive symptoms in schizophrenia but does not eliminate them

- Can improve negative symptoms, as well as aggressive, cognitive, and affective symptoms in schizophrenia
- Most schizophrenic patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third
- Perhaps 5–15% of schizophrenic patients can experience an overall improvement of greater than 50–60%, especially when receiving stable treatment for more than a year
- Such patients are considered super-responders or “awakeners” since they may be well enough to be employed, live independently, and sustain long-term relationships
- Continue treatment until reaching a plateau of improvement
- After reaching a satisfactory plateau, continue treatment for at least a year after first episode of psychosis
- For second and subsequent episodes of psychosis, treatment may need to be indefinite
- Even for first episodes of psychosis, it may be preferable to continue treatment indefinitely to avoid subsequent episodes

If It Doesn't Work

- Try one of the other first-line atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, asenapine, iloperidone, lurasidone)
- If two or more antipsychotic monotherapies do not work, consider clozapine
- Some patients may require treatment with a conventional antipsychotic
- If no atypical antipsychotic is effective, consider higher doses or augmentation with valproate or lamotrigine
- Consider noncompliance and switch to another antipsychotic with fewer side effects or to an antipsychotic that can be given by depot injection
- Consider initiating rehabilitation and psychotherapy such as cognitive remediation
- Consider presence of concomitant drug abuse

**Best Augmenting Combos for Partial Response or Treatment Resistance**

- Valproic acid (valproate, divalproex, divalproex ER)
- Augmentation of amisulpride has not been systematically studied

- Other mood-stabilizing anticonvulsants (carbamazepine, oxcarbazepine, lamotrigine)
- Lithium
- Benzodiazepines

Tests

✳ Although risk of diabetes and dyslipidemia with amisulpride has not been systematically studied, monitoring as for all other atypical antipsychotics is suggested

Before starting an atypical antipsychotic

✳ Weigh all patients and track BMI during treatment

- Get baseline personal and family history of diabetes, obesity, dyslipidemia, hypertension, and cardiovascular disease
- Get waistline circumference (at umbilicus), blood pressure, fasting plasma glucose, and fasting lipid profile
- Determine if patient is
 - overweight (BMI 25.0–29.9)
 - obese (BMI ≥30)
 - has pre-diabetes (fasting plasma glucose 100–125 mg/dL)
 - has diabetes (fasting plasma glucose >126 mg/dL)
 - has hypertension (BP >140/90 mm Hg)
 - has dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol)
- Treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management

Monitoring after starting an atypical antipsychotic

✳ BMI monthly for 3 months, then quarterly

- Consider monitoring fasting triglycerides monthly for several months in patients at high risk for metabolic complications and when initiating or switching antipsychotics
- Blood pressure, fasting plasma glucose, fasting lipids within 3 months and then annually, but earlier and more frequently for patients with diabetes or who have gained >5% initial weight
- Treat or refer for treatment and consider switching to another atypical antipsychotic for patients who become overweight, obese, pre-diabetic, diabetic, hypertensive, or dyslipidemic while receiving an atypical antipsychotic

- ✳ Even in patients without known diabetes, be vigilant for the rare but life-threatening onset of diabetic ketoacidosis, which always requires immediate treatment by monitoring for the rapid onset of polyuria, polydipsia, weight loss, nausea, vomiting, dehydration, rapid respiration, weakness and clouding of sensorium, even coma
- EKGs may be useful for selected patients (e.g., those with personal or family history of QTc prolongation; cardiac arrhythmia; recent myocardial infarction; uncompensated heart failure; or taking agents that prolong QTc interval such as pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin, etc.)
 - Patients at risk for electrolyte disturbances (e.g., patients on diuretic therapy) should have baseline and periodic serum potassium and magnesium measurements
 - Patients with low white blood cell count (WBC) or history of drug-induced leucopenia/neutropenia should have complete blood count (CBC) monitored frequently during the first few months and amisulpride should be discontinued at the first sign of decline of WBC in the absence of other causative factors

SIDE EFFECTS

How Drug Causes Side Effects

- By blocking dopamine 2 receptors in the striatum, it can cause motor side effects, especially at high doses
- By blocking dopamine 2 receptors in the pituitary, it can cause elevations in prolactin
- Mechanism of weight gain and possible increased incidence of diabetes and dyslipidemia with atypical antipsychotics is unknown

Notable Side Effects

- ✳ Extrapiramidal symptoms
- ✳ Galactorrhea, amenorrhea
- ✳ Atypical antipsychotics may increase the risk for diabetes and dyslipidemia, although the specific risks associated with amisulpride are unknown
- Insomnia, sedation, agitation, anxiety
 - Constipation, weight gain
 - Rare tardive dyskinesia



Life-Threatening or Dangerous Side Effects

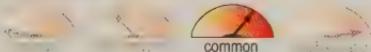
- Rare neuroleptic malignant syndrome
- Rare seizures
- Dose-dependent QTc prolongation
- Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis

Weight Gain



- Occurs in significant minority

Sedation



- Many experience and/or can be significant in amount, especially at high doses

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- For motor symptoms, add an anticholinergic agent
- Take more of the dose at bedtime to help reduce daytime sedation
- Weight loss, exercise programs, and medical management for high BMIs, diabetes, dyslipidemia
- Switch to another atypical antipsychotic

Best Augmenting Agents for Side Effects

- Benztrapine or trihexyphenidyl for motor side effects
- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- Schizophrenia: 400–800 mg/day in 2 doses
- Negative symptoms only: 50–300 mg/day
- Dysthymia: 50 mg/day

Dosage Forms

- Different formulations may be available in different markets
- Tablet 50 mg, 100 mg, 200 mg, 400 mg
- Oral solution 100 mg/mL

How to Dose

- Initial 400–800 mg/day in 2 doses; daily doses above 400 mg should be divided in 2; maximum generally 1200 mg/day
- See also the Switching section below, after Pearls



Dosing Tips

- Efficacy for negative symptoms in schizophrenia may be achieved at lower doses, while efficacy for positive symptoms may require higher doses
- Patients receiving low doses may only need to take the drug once daily
- For dysthymia and depression, use only low doses
- Dose-dependent QTc prolongation, so use with caution, especially at higher doses (>800 mg/day)
- Amisulpride may accumulate in patients with renal insufficiency, requiring lower dosing or switching to another antipsychotic to avoid QTc prolongation in these patients
- Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³

Overdose

- Sedation, coma, hypotension, extrapyramidal symptoms

Long-Term Use

- Amisulpride is used for both acute and chronic schizophrenia treatment

Habit Forming

- No

How to Stop

- See Switching section of individual agents for how to stop amisulpride
- Rapid discontinuation may lead to rebound psychosis and worsening of symptoms

Pharmacokinetics

- Elimination half-life approximately 12 hours
- Excreted largely unchanged



Drug Interactions

- Can decrease the effects of levodopa, dopamine agonists
- Can increase the effects of antihypertensive drugs

- CNS effects may be increased if used with a CNS depressant
- May enhance QTc prolongation of other drugs capable of prolonging QTc interval
- Since amisulpride is only weakly metabolized, few drug interactions that could raise amisulpride plasma levels are expected



Other Warnings/ Precautions

- Use cautiously in patients with alcohol withdrawal or convulsive disorders because of possible lowering of seizure threshold
- If signs of neuroleptic malignant syndrome develop, treatment should be immediately discontinued
- Because amisulpride may dose-dependently prolong QTc interval, use with caution in patients who have bradycardia or who are taking drugs that can induce bradycardia (e.g., beta blockers, calcium channel blockers, clonidine, digitalis)
- Because amisulpride may dose-dependently prolong QTc interval, use with caution in patients who have hypokalemia and/or hypomagnesemia or who are taking drugs that can induce hypokalemia and/or magnesemia (e.g., diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactide)
- Use only with caution if at all in Parkinson's disease or Lewy body dementia, especially at high doses

Do Not Use

- If patient has pheochromocytoma
- If patient has prolactin-dependent tumor
- If patient is pregnant or nursing
- If patient is taking agents capable of significantly prolonging QTc interval (e.g., pimozide; thioridazine; selected antiarrhythmics such as quinidine, disopyramide, amiodarone, and sotalol; selected antibiotics such as moxifloxacin and sparfloxacin)
- If there is a history of QTc prolongation or cardiac arrhythmia, recent acute myocardial infarction, uncompensated heart failure
- If patient is taking cisapride, intravenous erythromycin, or pentamidine
- In children
- If there is a proven allergy to amisulpride

SPECIAL POPULATIONS

Renal Impairment

- Use with caution; drug may accumulate
- Amisulpride is eliminated by the renal route; in cases of severe renal insufficiency, the dose should be decreased and intermittent treatment or switching to another antipsychotic should be considered

Hepatic Impairment

- Use with caution, but dose adjustment not generally necessary

Cardiac Impairment

- Amisulpride produces a dose-dependent prolongation of QTc interval, which may be enhanced by the existence of bradycardia, hypokalemia, congenital or acquired long QTc interval, which should be evaluated prior to administering amisulpride
- Use with caution if treating concomitantly with a medication likely to produce prolonged bradycardia, hypokalemia, slowing of intracardiac conduction, or prolongation of the QTc interval
- Avoid amisulpride in patients with a known history of QTc prolongation, recent acute myocardial infarction, and uncompensated heart failure

Elderly

- Some patients may be more susceptible to sedative and hypotensive effects
- Although atypical antipsychotics are commonly used for behavioral disturbances in dementia, no agent has been approved for treatment of elderly patients with dementia-related psychosis
- Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo, and also have an increased risk of cerebrovascular events



Children and Adolescents

- Efficacy and safety not established under age 18



Pregnancy

- Although animal studies have not shown teratogenic effect, amisulpride is not recommended for use during pregnancy

- There is a risk of abnormal muscle movements and withdrawal symptoms in newborns whose mothers took an antipsychotic during the third trimester; symptoms may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty feeding
- Psychotic symptoms may worsen during pregnancy and some form of treatment may be necessary

Breast Feeding

- Unknown if amisulpride is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- ✿ Recommended either to discontinue drug or bottle feed

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Not as clearly associated with weight gain as some other atypical antipsychotics
- For patients who are responsive to low-dose activation effects that reduce negative symptoms and depression

Potential Disadvantages

- Patients who have difficulty being compliant with twice daily dosing
- Patients for whom elevated prolactin may not be desired (e.g., possibly pregnant patients; pubescent girls with amenorrhea; postmenopausal women with low estrogen who do not take estrogen replacement therapy)
- Patients with severe renal impairment

Primary Target Symptoms

- Positive symptoms of psychosis
- Negative symptoms of psychosis
- Depressive symptoms



Pearls

- ✿ Efficacy has been particularly well demonstrated in patients with predominantly negative symptoms

- ✿ The increase in prolactin caused by amisulpride may cause menstruation to stop
- Some treatment-resistant patients with inadequate responses to clozapine may benefit from amisulpride augmentation of clozapine
- Risks of diabetes and dyslipidemia not well studied, but does not seem to cause as much weight gain as some other atypical antipsychotics
- Has atypical antipsychotic properties (i.e., antipsychotic action without a high incidence of extrapyramidal symptoms), especially at low doses, but not a serotonin dopamine antagonist
- Mediates its atypical antipsychotic properties via novel actions on dopamine receptors, perhaps dopamine stabilizing partial agonist actions on dopamine 2 receptors
- May be more of a dopamine 2 antagonist than aripiprazole, but less of a dopamine 2 antagonist than other atypical or conventional antipsychotics
- Low-dose activating actions may be beneficial for negative symptoms in schizophrenia
- Very low doses may be useful in dysthymia
- Compared to sulpiride, amisulpride has better oral bioavailability and more potency, thus allowing lower dosing, less weight gain, and fewer extrapyramidal symptoms
- Compared to other atypical antipsychotics with potent serotonin 2A antagonism, amisulpride may have more extrapyramidal symptoms and prolactin elevation, but may still be classified as an atypical antipsychotic, particularly at low doses
- Patients have very similar antipsychotic responses to any conventional antipsychotic, which is different from atypical antipsychotics where antipsychotic responses of individual patients can occasionally vary greatly from one atypical antipsychotic to another
- Patients with inadequate responses to atypical antipsychotics may benefit from determination of plasma drug levels and, if low, a dosage increase even beyond the usual prescribing limits
- Patients with inadequate responses to atypical antipsychotics may also benefit from a trial of augmentation with a

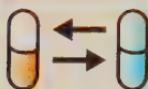
conventional antipsychotic or switching to a conventional antipsychotic

- However, long-term polypharmacy with a combination of a conventional antipsychotic with an atypical antipsychotic may combine their side effects without clearly augmenting the efficacy of either
- For treatment-resistant patients, especially those with impulsivity, aggression, violence, and self-harm, long-term polypharmacy with

2 atypical antipsychotics or with 1 atypical antipsychotic and 1 conventional antipsychotic may be useful or even necessary while closely monitoring

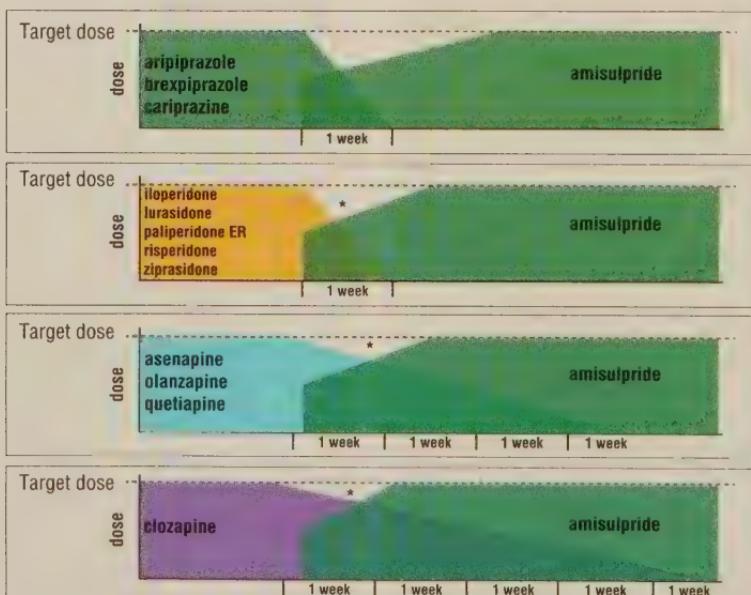
- In such cases, it may be beneficial to combine 1 depot antipsychotic with 1 oral antipsychotic
- Although a frequent practice by some prescribers, adding two conventional antipsychotics together has little rationale and may reduce tolerability without clearly enhancing efficacy

THE ART OF SWITCHING



Switching from Oral Antipsychotics to Amisulpride

- It is advisable to begin amisulpride at an intermediate dose and build the dose rapidly over 3–7 days
- Clinical experience has shown that asenapine, quetiapine, and olanzapine should be tapered off slowly over a period of 3–4 weeks, to allow patients to readapt to the withdrawal of blocking cholinergic, histaminergic, and alpha-1 receptors
- Clozapine should always be tapered off slowly, over a period of 4 weeks or more
- Benzodiazepine or anticholinergic medication can be administered during cross-titration to help alleviate side effects such as insomnia, agitation, and/or psychosis





Suggested Reading

Burns T, Bale R. Clinical advantages of amisulpride in the treatment of acute schizophrenia. *J Int Med Res* 2001;29(6): 451–66.

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Komossa K, Rummel-Kluge C, Hunder H, et al. Amisulpride versus other atypical

antipsychotics for schizophrenia. *Cochrane Database Syst Rev* 2010;(1):CD006624.

Leucht S, Pitschel-Walz G, Engel RR, Kissling W. Amisulpride, an unusual “atypical” antipsychotic: a meta-analysis of randomized controlled trials. *Am J Psychiatry* 2002;159(2):180–90.

THERAPEUTICS

Brands • Elavil

see index for additional brand names

Generic? Yes**Class**

- Neuroscience-based Nomenclature: serotonin, norepinephrine multi-modal (SN-MM)
- Tricyclic antidepressant (TCA)
- Serotonin and norepinephrine/noradrenaline reuptake inhibitor

Commonly Prescribed for

(bold for FDA approved)

- Depression
- Endogenous depression
- **Neuropathic pain/chronic pain**
- **Fibromyalgia**
- **Headache**
- **Low back pain/neck pain**
- Anxiety
- Insomnia
- Treatment-resistant depression

**How the Drug Works**

- Boosts neurotransmitters serotonin and norepinephrine/noradrenaline
- Blocks serotonin reuptake pump (serotonin transporter), presumably increasing serotonergic neurotransmission
- Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing noradrenergic neurotransmission
- Presumably desensitizes both serotonin 1A receptors and beta adrenergic receptors
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, amitriptyline can increase dopamine neurotransmission in this part of the brain

How Long Until It Works

- May have immediate effects in treating insomnia or anxiety
- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all

- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment of depression is complete remission of current symptoms as well as prevention of future relapses
- The goal of treatment of chronic pain conditions such as neuropathic pain, fibromyalgia, headaches, low back pain, and neck pain is to reduce symptoms as much as possible, especially in combination with other treatments
- Treatment of depression most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Treatment of chronic pain conditions such as neuropathic pain, fibromyalgia, headache, low back pain, and neck pain may reduce symptoms, but rarely eliminates them completely, and is not a cure since symptoms can recur after medicine is stopped
- Continue treatment of depression until all symptoms are gone (remission)
- Once symptoms of depression are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders and chronic pain conditions such as neuropathic pain, fibromyalgia, headache, low back pain, and neck pain may also need to be indefinite, but long-term treatment is not well studied in these conditions

If It Doesn't Work

- Many depressed patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other depressed patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)

- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer



Best Augmenting Combos for Partial Response or Treatment Resistance

- Lithium, buspirone, thyroid hormone (for depression)
- Gabapentin, tiagabine, other anticonvulsants, even opiates if done by experts while monitoring carefully in difficult cases (for chronic pain)

Tests

- Baseline ECG is recommended for patients over age 50
- Since tricyclic and tetracyclic antidepressants are frequently associated with weight gain, before starting treatment, weigh all patients and determine if the patient is already overweight (BMI 25.0–29.9) or obese (BMI ≥ 30)
- Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–125 mg/dL), diabetes (fasting plasma glucose > 126 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management
- Monitor weight and BMI during treatment
- While giving a drug to a patient who has gained $> 5\%$ of initial weight, consider evaluating for the presence of pre-diabetes, diabetes, or dyslipidemia, or consider switching to a different antidepressant
- EKGs may be useful for selected patients (e.g., those with personal or family history of QTc prolongation; cardiac arrhythmia; recent myocardial infarction; uncompensated heart failure; or taking agents that prolong QTc interval such as pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin, etc.)
- Patients at risk for electrolyte disturbances (e.g., patients on diuretic therapy) should have baseline and periodic serum potassium and magnesium measurements

SIDE EFFECTS

How Drug Causes Side Effects

- Anticholinergic activity may explain sedative effects, dry mouth, constipation, and blurred vision
- Sedative effects and weight gain may be due to antihistamine properties
- Blockade of alpha adrenergic 1 receptors may explain dizziness, sedation, and hypotension
- Cardiac arrhythmias and seizures, especially in overdose, may be caused by blockade of ion channels

Notable Side Effects

- Blurred vision, constipation, urinary retention, increased appetite, dry mouth, nausea, diarrhea, heartburn, unusual taste in mouth, weight gain
- Fatigue, weakness, dizziness, sedation, headache, anxiety, nervousness, restlessness
- Sexual dysfunction (impotence, change in libido)
- Sweating, rash, itching



Life-Threatening or Dangerous Side Effects

- Paralytic ileus, hyperthermia (TCAs + anticholinergic agents)
- Lowered seizure threshold and rare seizures
- Orthostatic hypotension, sudden death, arrhythmias, tachycardia
- QTc prolongation
- Hepatic failure, extrapyramidal symptoms
- Increased intraocular pressure
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Many experience and/or can be significant in amount
- Can increase appetite and carbohydrate craving

Sedation



- Many experience and/or can be significant in amount
- Tolerance to sedative effects may develop with long-term use

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- Switch to an SSRI or newer antidepressant

Best Augmenting Agents for Side Effects

- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 50–150 mg/day

Dosage Forms

- Capsule 25 mg, 50 mg, 100 mg

How to Dose

- Initial 25 mg/day at bedtime; increase by 25 mg every 3–7 days
- 75 mg/day in divided doses; increase to 150 mg/day; maximum 300 mg/day



Dosing Tips

- If given in a single dose, should generally be administered at bedtime because of its sedative properties
- If given in split doses, largest dose should generally be given at bedtime because of its sedative properties
- If patients experience nightmares, split dose and do not give large dose at bedtime
- Patients treated for chronic pain may only require lower doses
- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar disorder, and switch to a mood stabilizer or an atypical antipsychotic

Overdose

- Death may occur; CNS depression, convulsions, cardiac dysrhythmias, severe hypotension, EKG changes, coma

Long-Term Use

- Safe

Habit Forming

- No

How to Stop

- Taper to avoid withdrawal effects
- Even with gradual dose reduction, some withdrawal symptoms may appear within the first 2 weeks
- Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation
- If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly

Pharmacokinetics

- Substrate for CYP450 2D6 and 1A2
- Plasma half-life 10–28 hours
- Metabolized to an active metabolite, nortriptyline, which is predominantly a norepinephrine reuptake inhibitor, by demethylation via CYP450 1A2
- Food does not affect absorption



Drug Interactions

- Tramadol increases the risk of seizures in patients taking TCAs
- Use of TCAs with anticholinergic drugs may result in paralytic ileus or hyperthermia
- Fluoxetine, paroxetine, bupropion, duloxetine, and other CYP450 2D6 inhibitors may increase TCA concentrations
- Fluvoxamine, a CYP450 1A2 inhibitor, can decrease the conversion of amitriptyline to nortriptyline and increase amitriptyline plasma concentrations
- Cimetidine may increase plasma concentrations of TCAs and cause anticholinergic symptoms
- Phenothiazines or haloperidol may raise TCA blood concentrations
- May alter effects of antihypertensive drugs; may inhibit hypotensive effects of clonidine
- Use of TCAs with sympathomimetic agents may increase sympathetic activity

- Methylphenidate may inhibit metabolism of TCAs
- Activation and agitation, especially following switching or adding antidepressants, may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of amitriptyline



Other Warnings/ Precautions

- Add or initiate other antidepressants with caution for up to 2 weeks after discontinuing amitriptyline
- Generally, do not use with MAOIs, including 14 days after MAOIs are stopped; do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing amitriptyline, but see Pearls
- Use with caution in patients with history of seizures, urinary retention, angle-closure glaucoma, hyperthyroidism
- TCAs can increase QTc interval, especially at toxic doses, which can be attained not only by overdose but also by combining with drugs that inhibit TCA metabolism via CYP450 2D6, potentially causing torsade de pointes-type arrhythmia or sudden death
- Because TCAs can prolong QTc interval, use with caution in patients who have bradycardia or who are taking drugs that can induce bradycardia (e.g., beta blockers, calcium channel blockers, clonidine, digitalis)
- Because TCAs can prolong QTc interval, use with caution in patients who have hypokalemia and/or hypomagnesemia, or who are taking drugs that can induce hypokalemia and/or magnesemia (e.g., diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactide)
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies

- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is recovering from myocardial infarction
- If patient is taking agents capable of significantly prolonging QTc interval (e.g., pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin)
- If there is a history of QTc prolongation or cardiac arrhythmia, recent acute myocardial infarction, uncompensated heart failure
- If patient is taking drugs that inhibit TCA metabolism, including CYP450 2D6 inhibitors, except by an expert
- If there is reduced CYP450 2D6 function, such as patients who are poor 2D6 metabolizers, except by an expert and at low doses
- If there is a proven allergy to amitriptyline or nortriptyline

SPECIAL POPULATIONS

Renal Impairment

- Use with caution; may need to lower dose

Hepatic Impairment

- Use with caution; may need to lower dose

Cardiac Impairment

- Baseline ECG is recommended
- TCAs have been reported to cause arrhythmias, prolongation of conduction time, orthostatic hypotension, sinus tachycardia, and heart failure, especially in the diseased heart
- Myocardial infarction and stroke have been reported with TCAs
- TCAs produce QTc prolongation, which may be enhanced by the existence of bradycardia, hypokalemia, congenital or acquired long QTc interval, which should be evaluated prior to administering amitriptyline
- Use with caution if treating concomitantly with a medication likely to produce prolonged bradycardia, hypokalemia,

- slowing of intracardiac conduction, or prolongation of the QTc interval
 - Avoid TCAs in patients with a known history of QTc prolongation, recent acute myocardial infarction, and uncompensated heart failure
 - TCAs may cause a sustained increase in heart rate in patients with ischemic heart disease and may worsen (decrease) heart rate variability, an independent risk of mortality in cardiac populations
 - Since SSRIs may improve (increase) heart rate variability in patients following a myocardial infarct and may improve survival as well as mood in patients with acute angina or following a myocardial infarction, these are more appropriate agents for cardiac population than tricyclic/tetracyclic antidepressants
- * Risk/benefit ratio may not justify use of TCAs in cardiac impairment**

Elderly

- Baseline ECG is recommended for patients over age 50
- May be more sensitive to anticholinergic, cardiovascular, hypotensive, and sedative effects
- Initial dose 50 mg/day; increase gradually up to 100 mg/day
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Not generally recommended for use under age 12
- Several studies show lack of efficacy of TCAs for depression

- May be used to treat enuresis or hyperactive/impulsive behaviors
- Some cases of sudden death have occurred in children taking TCAs
- Adolescents: initial dose 50 mg/day; increase gradually up to 100 mg/day



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Crosses the placenta
- Adverse effects have been reported in infants whose mothers took a TCA (lethargy, withdrawal symptoms, fetal malformations)
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy

Breast Feeding

- Some drug is found in mother's breast milk
- * Recommended either to discontinue drug or bottle feed**
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY**Potential Advantages**

- Patients with insomnia
- Severe or treatment-resistant depression
- Patients with a wide variety of chronic pain syndromes

Potential Disadvantages

- Pediatric and geriatric patients
- Patients concerned with weight gain
- Cardiac patients

Primary Target Symptoms

- Depressed mood
- Symptoms of anxiety
- Somatic symptoms
- Chronic pain
- Insomnia

**Pearls**

- Was once one of the most widely prescribed agents for depression
- Remains one of the most favored TCAs for treating headache and a wide variety of chronic pain syndromes, including neuropathic pain, fibromyalgia, migraine, neck pain, and low back pain
- Preference of some prescribers for amitriptyline over other tricyclic/tetracyclic antidepressants for the treatment of chronic pain syndromes is based more upon art and anecdote rather than controlled clinical trials, since many TCAs/tetracyclines may be effective for chronic pain syndromes
- TCAs are no longer generally considered a first-line treatment option for depression because of their side effect profile
- Amitriptyline has been shown to be effective in primary insomnia
- TCAs may aggravate psychotic symptoms
- Alcohol should be avoided because of additive CNS effects
- Underweight patients may be more susceptible to adverse cardiovascular effects
- Children, patients with inadequate hydration, and patients with cardiac

disease may be more susceptible to TCA-induced cardiotoxicity than healthy adults

- For the expert only: although generally prohibited, a heroic but potentially dangerous treatment for severely treatment-resistant patients is to give a tricyclic/tetracyclic antidepressant other than clomipramine simultaneously with an MAOI for patients who fail to respond to numerous other antidepressants
- If this option is elected, start the MAOI with the tricyclic/tetracyclic antidepressant simultaneously at low doses after appropriate drug washout, then alternately increase doses of these agents every few days to a week as tolerated
- Although very strict dietary and concomitant drug restrictions must be observed to prevent hypertensive crises and serotonin syndrome, the most common side effects of MAOI/tricyclic or tetracyclic combinations may be weight gain and orthostatic hypotension
- Patients on TCAs should be aware that they may experience symptoms such as photosensitivity or blue-green urine
- SSRIs may be more effective than TCAs in women, and TCAs may be more effective than SSRIs in men
- Since tricyclic/tetracyclic antidepressants are substrates for CYP450 2D6, and 7% of the population (especially Caucasians) may have a genetic variant leading to reduced activity of 2D6, such patients may not safely tolerate normal doses of tricyclic/tetracyclic antidepressants and may require dose reduction
- Phenotypic testing may be necessary to detect this genetic variant prior to dosing with a tricyclic/tetracyclic antidepressant, especially in vulnerable populations such as children, elderly, cardiac populations, and those on concomitant medications
- Patients who seem to have extraordinarily severe side effects at normal or low doses may have this phenotypic CYP450 2D6 variant and require low doses or switching to another antidepressant not metabolized by 2D6



Suggested Reading

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THERAPEUTICS

Brands • Asendin

see index for additional brand names

Generic? Yes**Class**

- Neuroscience-based Nomenclature: norepinephrine, serotonin reuptake inhibitor (SN-RI)
- Tricyclic antidepressant (TCA), sometimes classified as a tetracyclic antidepressant
- Norepinephrine/noradrenaline reuptake inhibitor
- Serotonin 2A antagonist
- Parent drug and especially an active metabolite are dopamine 2 antagonists

Commonly Prescribed for

(bold for FDA approved)

- **Neurotic or reactive depressive disorder**
- **Endogenous and psychotic depressions**
- Depression accompanied by anxiety or agitation
- Depressive phase of bipolar disorder
- Anxiety
- Insomnia
- Neuropathic pain/chronic pain
- Treatment-resistant depression

**How the Drug Works**

- Boosts neurotransmitter norepinephrine/noradrenaline
- Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing noradrenergic neurotransmission
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, amoxapine can thus increase dopamine neurotransmission in this part of the brain
- A more potent inhibitor of norepinephrine reuptake pump than serotonin reuptake pump (serotonin transporter)
- At high doses may also boost neurotransmitter serotonin and presumably increase serotonergic neurotransmission
- Blocks dopamine 2 receptors, reducing positive symptoms of psychosis

How Long Until It Works

- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Continue treatment until all symptoms are gone (remission)
- Once symptoms gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders may also need to be indefinite

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer

**Best Augmenting Combos
for Partial Response or
Treatment Resistance**

- Lithium, buspirone, thyroid hormone

Tests

- Baseline ECG is recommended for patients over age 50

- Since tricyclic and tetracyclic antidepressants are frequently associated with weight gain, before starting treatment, weigh all patients and determine if the patient is already overweight (BMI 25.0–29.9) or obese (BMI ≥30)
- Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–125 mg/dL), diabetes (fasting plasma glucose >126 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management
- Monitor weight and BMI during treatment
- While giving a drug to a patient who has gained >5% of initial weight, consider evaluating for the presence of pre-diabetes, diabetes, or dyslipidemia, or consider switching to a different antidepressant
- EKGs may be useful for selected patients (e.g., those with personal or family history of QTc prolongation; cardiac arrhythmia; recent myocardial infarction; uncompensated heart failure; or taking agents that prolong QTc interval such as pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin, etc.)
- Patients at risk for electrolyte disturbances (e.g., patients on diuretic therapy) should have baseline and periodic serum potassium and magnesium measurements

SIDE EFFECTS

How Drug Causes Side Effects

- Anticholinergic activity may explain sedative effects, dry mouth, constipation, and blurred vision
- Sedative effects and weight gain may be due to antihistamine properties
- Blockade of alpha adrenergic 1 receptors may explain dizziness, sedation, and hypotension
- Cardiac arrhythmias and seizures, especially in overdose, may be caused by blockade of ion channels

Notable Side Effects

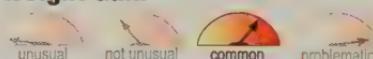
- Blurred vision, constipation, urinary retention, increased appetite, dry mouth, nausea, diarrhea, heartburn, unusual taste in mouth, weight gain
- Fatigue, weakness, dizziness, sedation, headache, anxiety, nervousness, restlessness
- Sexual dysfunction, sweating
- Can cause extrapyramidal symptoms, akathisia, and theoretically, tardive dyskinesia



Life-Threatening or Dangerous Side Effects

- Paralytic ileus, hyperthermia (TCAs/tetracyclines + anticholinergic agents)
- Lowered seizure threshold and rare seizures
- Orthostatic hypotension, sudden death, arrhythmias, tachycardia
- QTc prolongation
- Hepatic failure, extrapyramidal symptoms
- Increased intraocular pressure
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Many experience and/or can be significant in amount
- Can increase appetite and carbohydrate craving

Sedation



- Many experience and/or can be significant in amount
- Tolerance to sedative effect may develop with long-term use

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- Switch to an SSRI or newer antidepressant

Best Augmenting Agents for Side Effects

- Many side effects cannot be improved with an augmenting agent
- May use anticholinergics for extrapyramidal symptoms, or switch to another antidepressant

DOSING AND USE

Usual Dosage Range

- 200–300 mg/day

Dosage Forms

- Tablets 25 mg, 50 mg, 100 mg, 150 mg

How to Dose

- Initial 25 mg 2–3 times/day; increase gradually to 100 mg 2–3 times/day or a single dose at bedtime; maximum 400 mg/day (may dose up to 600 mg/day in inpatients)



Dosing Tips

- If given in a single dose, should generally be administered at bedtime because of its sedative properties
- If given in split doses, largest dose should generally be given at bedtime because of its sedative properties
- If patients experience nightmares, split dose and do not give large dose at bedtime
- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar disorder, and switch to a mood stabilizer or an atypical antipsychotic

Overdose

- Death may occur; convulsions, cardiac dysrhythmias, severe hypotension, CNS depression, coma, changes in EKG

Long-Term Use

- Generally safe
- Some patients may develop withdrawal dyskinesias when discontinuing amoxapine after long-term use

Habit Forming

- Some patients may develop tolerance

How to Stop

- Taper to avoid withdrawal effects
- Even with gradual dose reduction some withdrawal symptoms may appear within the first 2 weeks
- Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation
- If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly

Pharmacokinetics

- Substrate for CYP450 2D6
- Half-life of parent drug approximately 8 hours
- * 7- and 8-hydroxymetabolites are active and possess serotonin 2A and dopamine 2 antagonist properties, similar to atypical antipsychotics
- * Amoxapine is the *N*-desmethyl metabolite of the conventional antipsychotic loxapine
- Half-life of the active metabolites approximately 24 hours



Drug Interactions

- Tramadol increases the risk of seizures in patients taking TCAs
- Use of TCAs/tetracyclines with anticholinergic drugs may result in paralytic ileus or hyperthermia
- Fluoxetine, paroxetine, bupropion, duloxetine, and other CYP450 2D6 inhibitors may increase TCA/tetracyclic concentrations
- Cimetidine may increase plasma concentrations of TCAs/tetracyclines and cause anticholinergic symptoms
- Phenothiazines or haloperidol may raise TCA/tetracyclic blood concentrations
- May alter effects of antihypertensive drugs; may inhibit hypotensive effects of clonidine
- Use of TCAs/tetracyclines with sympathomimetic agents may increase sympathetic activity
- Methylphenidate may inhibit metabolism of TCAs/tetracyclines
- Activation and agitation, especially following switching or adding antidepressants, may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal

ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of amoxapine



Other Warnings/ Precautions

- Add or initiate other antidepressants with caution for up to 2 weeks after discontinuing amoxapine
- Generally, do not use with MAOIs, including 14 days after MAOIs are stopped; do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing amoxapine, but see Pearls
- Use with caution in patients with history of seizure, urinary retention, angle-closure glaucoma, hyperthyroidism
- TCAs/tetracyclics can increase QTc interval, especially at toxic doses, which can be attained not only by overdose but also by combining with drugs that inhibit its metabolism via CYP450 2D6, potentially causing torsade de pointes-type arrhythmia or sudden death
- Because TCAs/tetracyclics can prolong QTc interval, use with caution in patients who have bradycardia or who are taking drugs that can induce bradycardia (e.g., beta blockers, calcium channel blockers, clonidine, digitalis)
- Because TCAs/tetracyclics can prolong QTc interval, use with caution in patients who have hypokalemia and/or hypomagnesemia, or who are taking drugs that can induce hypokalemia and/or magnesemia (e.g., diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactide)
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is recovering from myocardial infarction
- If patient is taking agents capable of significantly prolonging QTc interval (e.g., pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin)
- If there is a history of QTc prolongation or cardiac arrhythmia, recent acute myocardial infarction, uncompensated heart failure
- If patient is taking drugs that inhibit TCA/tetracyclic metabolism, including CYP450 2D6 inhibitors, except by an expert
- If there is reduced CYP450 2D6 function, such as patients who are poor 2D6 metabolizers, except by an expert and at low doses
- If there is a proven allergy to amoxapine or loxapine

SPECIAL POPULATIONS

Renal Impairment

- Use with caution – may require lower than usual adult dose

Hepatic Impairment

- Use with caution – may require lower than usual adult dose

Cardiac Impairment

- Baseline ECG is recommended
- TCAs/tetracyclics have been reported to cause arrhythmias, prolongation of conduction time, orthostatic hypotension, sinus tachycardia, and heart failure, especially in the diseased heart
- Myocardial infarction and stroke have been reported with TCAs/tetracyclics
- TCAs/tetracyclics produce QTc prolongation, which may be enhanced by the existence of bradycardia, hypokalemia, congenital or acquired long QTc interval, which should be evaluated prior to administering amoxapine
- Use with caution if treating concomitantly with a medication likely to produce prolonged bradycardia, hypokalemia, slowing of intracardiac conduction, or prolongation of the QTc interval
- Avoid TCAs/tetracyclics in patients with a known history of QTc prolongation, recent acute myocardial infarction, and uncompensated heart failure

- TCAs/tetracyclics may cause a sustained increase in heart rate in patients with ischemic heart disease and may worsen (decrease) heart rate variability, an independent risk of mortality in cardiac populations
- Since SSRIs may improve (increase) heart rate variability in patients following a myocardial infarct and may improve survival as well as mood in patients with acute angina or following a myocardial infarction, these are more appropriate agents for cardiac population than tricyclic/tetracyclic antidepressants

* Risk/benefit ratio may not justify use of TCAs/tetracyclics in cardiac impairment

Elderly

- Baseline ECG is recommended for patients over age 50
- May be more sensitive to anticholinergic, cardiovascular, hypotensive, and sedative effects
- Initial dose 25 mg/day at bedtime; increase by 25 mg/day each week; maximum dose 300 mg/day



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Not generally recommended for use under age 16
- Several studies show lack of efficacy of TCAs/tetracyclics for depression
- May be used to treat enuresis or hyperactive/impulsive behaviors
- Some cases of sudden death have occurred in children taking TCAs/tetracyclics
- Adolescents: initial 25–50 mg/day; increase gradually to 100 mg/day in divided doses or single dose at bedtime



Pregnancy

- Controlled studies have not been conducted in pregnant women
- Some animal studies show adverse effects
- Amoxapine crosses the placenta
- Adverse effects have been reported in infants whose mothers took a TCA (lethargy, withdrawal symptoms, fetal malformations)
- Evaluate for treatment with an antidepressant with a better risk/benefit ratio

Breast Feeding

- Some drug is found in mother's breast milk
- Recommended either to discontinue drug or bottle feed
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Evaluate for treatment with an antidepressant with a better risk/benefit ratio

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Severe or treatment-resistant depression
- Treatment-resistant psychotic depression

Potential Disadvantages

- Pediatric and geriatric patients
- Patients concerned with weight gain
- Cardiac patients
- Patients with Parkinson's disease or tardive dyskinesia

Primary Target Symptoms

- Depressed mood



Pearls

- Tricyclic/tetracyclic antidepressants are no longer generally considered a first-line treatment option for depression because of their side effect profile
- Tricyclic/tetracyclic antidepressants continue to be useful for severe or treatment-resistant depression

- ✿ Because of potential extrapyramidal symptoms, akathisia, and theoretical risk of tardive dyskinesia, first consider other TCAs/tetracyclics for long-term use in general and for treatment of chronic patients
- TCAs may aggravate psychotic symptoms
- Alcohol should be avoided because of additive CNS effects
- Underweight patients may be more susceptible to adverse cardiovascular effects
- Children, patients with inadequate hydration, and patients with cardiac disease may be more susceptible to TCA-induced cardiotoxicity than healthy adults
- For the expert only: although generally prohibited, a heroic but potentially dangerous treatment for severely treatment-resistant patients is to give a tricyclic/tetracyclic antidepressant other than clomipramine simultaneously with an MAOIs for patients who fail to respond to numerous other antidepressants
- Use of MAOIs with clomipramine is always prohibited because of the risk of serotonin syndrome and death
- Amoxapine may be the preferred tricyclic/tetracyclic antidepressant to combine with an MAOI in heroic cases due to its theoretically protective 5HT2A antagonist properties
- If this option is elected, start the MAOI with the tricyclic/tetracyclic antidepressant simultaneously at low doses after appropriate drug washout, then alternately increase doses of these agents every few days to a week as tolerated
- Although very strict dietary and concomitant drug restrictions must be observed to prevent hypertensive crises and serotonin syndrome, the most

- common side effects of MAOI/tricyclic or tetracyclic combinations may be weight gain and orthostatic hypotension
- Patients on TCAs/tetracyclics should be aware that they may experience symptoms such as photosensitivity or blue-green urine
- SSRIs may be more effective than TCAs/tetracyclics in women, and TCAs/tetracyclics may be more effective than SSRIs in men
- ✿ May cause some motor effects, possibly due to effects on dopamine receptors
- ✿ Amoxapine may have a faster onset of action than some other antidepressants
- ✿ May be pharmacologically similar to an atypical antipsychotic in some patients
- ✿ At high doses, patients who form high concentrations of active metabolites may have akathisia, extrapyramidal symptoms, and possibly develop tardive dyskinesia
- ✿ Structurally and pharmacologically related to the antipsychotic loxapine
- Since tricyclic/tetracyclic antidepressants are substrates for CYP450 2D6, and 7% of the population (especially Caucasians) may have a genetic variant leading to reduced activity of 2D6, such patients may not safely tolerate normal doses of tricyclic/tetracyclic antidepressants and may require dose reduction
- Phenotypic testing may be necessary to detect this genetic variant prior to dosing with a tricyclic/tetracyclic antidepressant, especially in vulnerable populations such as children, elderly, cardiac populations, and those on concomitant medications
- Patients who seem to have extraordinarily severe side effects at normal or low doses may have this phenotypic CYP450 2D6 variant and require low doses or switching to another antidepressant not metabolized by 2D6



Suggested Reading

Anderson IM. Meta-analytical studies on new antidepressants. Br Med Bull 2001; 57:161–78.

Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. J Aff Disorders 2000;58:19–36.

Hayes PE, Kristoff CA. Adverse reactions to five new antidepressants. Clin Pharm 1986; 5:471–80.

Jue SG, Dawson GW, Brogden RN. Amoxapine: a review of its pharmacology and efficacy in depressed states. Drugs 1982;24:1–23.

THERAPEUTICS

Brands

- Dexedrine
- Dexedrine Spansules
- Zenzedi
- ProCentra

see index for additional brand names

Generic? Yes



Class

- Neuroscience-based Nomenclature: dopamine, norepinephrine reuptake inhibitor and releaser (DN-RIRe)
- Stimulant

Commonly Prescribed for

(bold for FDA approved)

- Attention deficit hyperactivity disorder (ADHD) (ages 6 and older or 3 and older depending on formulation)**
- Narcolepsy (ages 12 and older or 6 and older depending on formulation)**
- Treatment-resistant depression



How the Drug Works

- Increases norepinephrine and especially dopamine actions by blocking their reuptake and facilitating their release
- Enhancement of dopamine and norepinephrine actions in certain brain regions may improve attention, concentration, executive function, and wakefulness (e.g., dorsolateral prefrontal cortex)
- Enhancement of dopamine actions in other brain regions (e.g., basal ganglia) may improve hyperactivity
- Enhancement of dopamine and norepinephrine in yet other brain regions (e.g., medial prefrontal cortex, hypothalamus) may improve depression, fatigue, and sleepiness

How Long Until It Works

- Some immediate effects can be seen with first dosing
- Can take several weeks to attain maximum therapeutic benefit

If It Works (for ADHD)

- The goal of treatment of ADHD is reduction of symptoms of inattentiveness, motor hyperactivity, and/or impulsiveness that disrupt social, school, and/or occupational functioning

- Continue treatment until all symptoms are under control or improvement is stable and then continue treatment indefinitely as long as improvement persists
- Reevaluate the need for treatment periodically
- Treatment for ADHD begun in childhood may need to be continued into adolescence and adulthood if continued benefit is documented

If It Doesn't Work (for ADHD)

- Consider adjusting dose or switching to another formulation of d-amphetamine or to another agent
 - Consider behavioral therapy
 - Consider the presence of noncompliance and counsel patient and parents
 - Consider evaluation for another diagnosis or for a comorbid condition (e.g., bipolar disorder, substance abuse, medical illness, etc.)
- * Some ADHD patients and some depressed patients may experience lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require either augmenting with a mood stabilizer or switching to a mood stabilizer



Best Augmenting Combos for Partial Response or Treatment Resistance

- Best to attempt other monotherapies prior to augmenting
- For the expert, can combine immediate-release formulation with a sustained-release formulation of d-amphetamine for ADHD
- For the expert, can combine with modafinil or atomoxetine for ADHD
- For the expert, can occasionally combine with atypical antipsychotics in highly treatment-resistant cases of bipolar disorder or ADHD
- For the expert, can combine with antidepressants to boost antidepressant efficacy in highly treatment-resistant cases of depression while carefully monitoring patient

Tests

- Before treatment, assess for presence of cardiac disease (history, family history, physical exam)
- Blood pressure should be monitored regularly
- In children, monitor weight and height

SIDE EFFECTS

How Drug Causes Side Effects

- Increases in norepinephrine peripherally can cause autonomic side effects, including tremor, tachycardia, hypertension, and cardiac arrhythmias
- Increases in norepinephrine and dopamine centrally can cause CNS side effects such as insomnia, agitation, psychosis, and substance abuse

Notable Side Effects

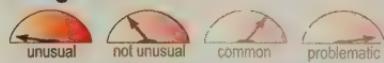
- * Insomnia, headache, exacerbation of tics, nervousness, irritability, overstimulation, tremor, dizziness
- Anorexia, nausea, dry mouth, constipation, diarrhea, weight loss
- Can temporarily slow normal growth in children (controversial)
- Sexual dysfunction long-term (impotence, libido changes) but can also improve sexual dysfunction short-term



Life-Threatening or Dangerous Side Effects

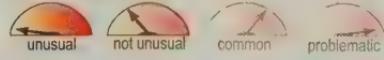
- Psychotic episodes, especially with parenteral abuse
- Seizures
- Palpitations, tachycardia, hypertension
- Rare activation of hypomania, mania, or suicidal ideation (controversial)
- Cardiovascular adverse effects, sudden death in patients with preexisting cardiac structural abnormalities

Weight Gain



- Reported but not expected
- Some patients may experience weight loss

Sedation



- Reported but not expected
- Activation much more common than sedation

What to Do About Side Effects

- Wait
- Adjust dose
- Switch to a long-acting stimulant
- Switch to another agent

- For insomnia, avoid dosing in afternoon/evening

Best Augmenting Agents for Side Effects

- Beta blockers for peripheral autonomic side effects
- Dose reduction or switching to another agent may be more effective since most side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- Narcolepsy: 5–60 mg/day (divided doses for tablet, once daily morning dose for Spansule capsule)
- ADHD: 5–40 mg/day (divided doses for tablet, once daily morning dose for Spansule capsule)

Dosage Forms

- Immediate-release tablet 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg
- Extended-release capsule 5 mg, 10 mg, 15 mg
- Immediate-release oral solution 5 mg/5 mL

How to Dose

- Narcolepsy, ages 12 and older (Spansule capsule or tablet): initial 10 mg/day; can increase by 10 mg each week; give first dose on waking; tablet is administered in divided doses
- Narcolepsy, ages 6 to 12 (tablet IR): initial 5 mg/day; can increase by 5 mg each week; administered in divided doses
- ADHD, ages 6 and older (Spansule capsule or tablet): initial 5 mg/day; can increase by 5 mg each week; give first dose on waking
- ADHD, ages 3 to 5 (tablet IR): Initial 2.5 mg/day; can increase by 2.5 mg each week; administered in divided doses



Dosing Tips

- Clinical duration of action often differs from pharmacokinetic half-life
- * Immediate-release dextroamphetamine has 3–6 hour duration of clinical action
- * Sustained-release dextroamphetamine (Dexedrine Spansule) has up to 8-hour duration of clinical action

- Tablets contain tartrazine, which may cause allergic reactions, particularly in patients allergic to aspirin
- Dexedrine Spansules are controlled-release and should therefore not be chewed but rather should only be swallowed whole
- ✿ Controlled-release delivery of dextroamphetamine may be sufficiently long in duration to allow elimination of lunchtime dosing in many but not all patients
- ✿ This innovation can be an important practical element in stimulant utilization, eliminating the hassle and pragmatic difficulties of lunchtime dosing at school, including storage problems, potential diversion, and the need for a medical professional to supervise dosing away from home
- Avoid dosing late in the day because of the risk of insomnia
- ✿ May be possible to dose only during the school week for some ADHD patients
- Off-label uses are dosed the same as for ADHD
- ✿ May be able to give drug holidays over the summer in order to reassess therapeutic utility and effects on growth and to allow catch-up from any growth suppression as well as to assess any other side effects and the need to reinstitute stimulant treatment for the next school term
- Side effects are generally dose-related
- Taking with food may delay peak actions for 2–3 hours

Overdose

- Rarely fatal; panic, hyperreflexia, rhabdomyolysis, rapid respiration, confusion, coma, hallucination, convulsion, arrhythmia, change in blood pressure, circulatory collapse

Long-Term Use

- Often used long-term for ADHD when ongoing monitoring documents continued efficacy
- Dependence and/or abuse may develop
- Tolerance to therapeutic effects may develop in some patients
- Long-term stimulant use may be associated with growth suppression in children (controversial)
- Periodic monitoring of weight, blood pressure, CBC, platelet counts, and liver function may be prudent

Habit Forming

- High abuse potential, Schedule II drug
- Patients may develop tolerance, psychological dependence

How to Stop

- Taper to avoid withdrawal effects
- Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder and may require follow-up and reinstitution of treatment
- Careful supervision is required during withdrawal from abusive use since severe depression may occur

Pharmacokinetics

- Half-life approximately 10–12 hours



Drug Interactions

- May affect blood pressure and should be used cautiously with agents used to control blood pressure
- Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid, ascorbic acid, fruit juices, etc.) and urinary acidifying agents (ammonium chloride, sodium phosphate, etc.) lower amphetamine plasma levels, so such agents can be useful to administer after an overdose but may also lower therapeutic efficacy of amphetamines
- Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) and urinary alkalinizing agents (acetazolamide, some thiazides) increase amphetamine plasma levels and potentiate amphetamine's actions
- Desipramine and protryptiline can cause striking and sustained increases in brain concentrations of d-amphetamine and may also add to d-amphetamine's cardiovascular effects
- Theoretically, other agents with norepinephrine reuptake blocking properties, such as venlafaxine, duloxetine, atomoxetine, milnacipran, and reboxetine, could also add to amphetamine's CNS and cardiovascular effects
- Amphetamines may counteract the sedative effects of antihistamines
- Haloperidol, chlorpromazine, and lithium may inhibit stimulatory effects of amphetamines
- Theoretically, atypical antipsychotics should also inhibit stimulatory effects of amphetamines

- Theoretically, amphetamines could inhibit the antipsychotic actions of antipsychotics
- Theoretically, amphetamines could inhibit the mood-stabilizing actions of atypical antipsychotics in some patients
- Combinations of amphetamines with mood stabilizers (lithium, anticonvulsants, atypical antipsychotics) is generally something for experts only, when monitoring patients closely and when other options fail
- Absorption of phenobarbital, phenytoin, and ethosuximide is delayed by amphetamines
- Amphetamines inhibit adrenergic blockers and enhance adrenergic effects of norepinephrine
- Amphetamines may antagonize hypotensive effects of veratrum alkaloids and other antihypertensives
- Amphetamines increase the analgesic effects of meperidine
- Amphetamines contribute to excessive CNS stimulation if used with large doses of propoxyphene
- Amphetamines can raise plasma corticosteroid levels
- MAOIs slow absorption of amphetamines and thus potentiate their actions, which can cause headache, hypertension, and rarely hypertensive crisis and malignant hyperthermia, sometimes with fatal results
- Use with MAOIs, including within 14 days of MAOI use, is not advised, but this can sometimes be considered by experts who monitor depressed patients closely when other treatment options for depression fail



Other Warnings/ Precautions

- Use with caution in patients with any degree of hypertension, hyperthyroidism, or history of drug abuse
- Children who are not growing or gaining weight should stop treatment, at least temporarily
- May worsen motor and phonic tics
- May worsen symptoms of thought disorder and behavioral disturbance in psychotic patients
- Stimulants have a high potential for abuse and must be used with caution in anyone with a current or past history of substance abuse or alcoholism or in emotionally unstable patients

- Administration of stimulants for prolonged periods of time should be avoided whenever possible or done only with close monitoring, as it may lead to marked tolerance and drug dependence, including psychological dependence with varying degrees of abnormal behavior
- Particular attention should be paid to the possibility of subjects obtaining stimulants for nontherapeutic use or distribution to others and the drugs should in general be prescribed sparingly with documentation of appropriate use
- Usual dosing has been associated with sudden death in children with structural cardiac abnormalities
- Not an appropriate first-line treatment for depression or for normal fatigue
- May lower the seizure threshold
- Emergence or worsening of activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of a mood stabilizer and/or discontinuation of d-amphetamine

Do Not Use

- If patient has extreme anxiety or agitation
- If patient has motor tics or Tourette's syndrome or if there is a family history of Tourette's, unless administered by an expert in cases when the potential benefits for ADHD outweigh the risks of worsening tics
- Should generally not be administered with an MAOI, including within 14 days of MAOI use, except in heroic circumstances and by an expert
- If patient has arteriosclerosis, cardiovascular disease, or severe hypertension
- If patient has glaucoma
- If patient has structural cardiac abnormalities
- If there is a proven allergy to any sympathomimetic agent

SPECIAL POPULATIONS

Renal Impairment

- No dose adjustment necessary

Hepatic Impairment

- Use with caution

Cardiac Impairment

- Use with caution, particularly in patients with recent myocardial infarction or other conditions that could be negatively affected by increased blood pressure
- Do not use in patients with structural cardiac abnormalities

Elderly

- Some patients may tolerate lower doses better



Children and Adolescents

- Safety and efficacy not established in children under age 3
- Use in young children should be reserved for the expert
- d-amphetamine may worsen symptoms of behavioral disturbance and thought disorder in psychotic children
- d-amphetamine has acute effects on growth hormone; long-term effects are unknown but weight and height should be monitored during long-term treatment
- Narcolepsy: ages 6–12: initial 5 mg/day; increase by 5 mg each week
- ADHD: ages 3–5: initial 2.5 mg/day; increase by 2.5 mg each week
- Sudden death in children and adolescents with serious heart problems has been reported
- American Heart Association recommends EKG prior to initiating stimulant treatment in children, although not all experts agree



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- There is a greater risk of premature birth and low birth weight in infants whose mothers take d-amphetamine during pregnancy

- Infants whose mothers take d-amphetamine during pregnancy may experience withdrawal symptoms
- In animal studies, d-amphetamine caused delayed skeletal ossification and decreased postweaning weight gain in rats; no major malformations occurred in rat or rabbit studies
- Use in women of childbearing potential requires weighing potential benefits to the mother against potential risks to the fetus
- For ADHD patients, d-amphetamine should generally be discontinued before anticipated pregnancies

Breast Feeding

- Some drug is found in mother's breast milk
- Recommended either to discontinue drug or bottle feed
- If infant shows signs of irritability, drug may need to be discontinued

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- May work in ADHD patients unresponsive to other stimulants
- Established long-term efficacy of immediate-release and Spansule formulations

Potential Disadvantages

- Patients with current or past substance abuse
- Patients with current or past bipolar disorder or psychosis

Primary Target Symptoms

- Concentration, attention span
- Motor hyperactivity
- Impulsiveness
- Physical and mental fatigue
- Daytime sleepiness
- Depression



Pearls

- May be useful for treatment of depressive symptoms in medically ill elderly patients
- May be useful for treatment of post-stroke depression
- A classical augmentation strategy for treatment-refractory depression

- ✿ Specifically, may be useful for treatment of cognitive dysfunction and fatigue as residual symptoms of major depressive disorder unresponsive to multiple prior treatments
- ✿ May also be useful for the treatment of cognitive impairment, depressive symptoms, and severe fatigue in patients with HIV infection and in cancer patients
- Can be used to potentiate opioid analgesia and reduce sedation, particularly in end-of-life management
- Some patients respond to or tolerate d-amphetamine better than methylphenidate and vice versa
- Some patients may benefit from an occasional addition of 5–10 mg of immediate-release d-amphetamine to their daily base of sustained-release Dexedrine Spansules
- ✿ Despite warnings, can be a useful adjunct to MAOIs for heroic treatment of highly refractory mood disorders when monitored with vigilance
- ✿ Can reverse sexual dysfunction caused by psychiatric illness and by some drugs such as SSRIs, including decreased libido, erectile dysfunction, delayed ejaculation, and anorgasmia
- Atypical antipsychotics may be useful in treating stimulant or psychotic consequences of overdose
- Taking with food may delay peak actions for 2–3 hours
- Half-life and duration of clinical action tend to be shorter in younger children
- Drug abuse may actually be lower in ADHD adolescents treated with stimulants than in ADHD adolescents who are not treated



Suggested Reading

Fry JM. Treatment modalities for narcolepsy. *Neurology* 1998;50(2 Suppl 1):S43–8.

Greenhill LL, Pliszka S, Dulcan MK, et al. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. *J Am Acad Child Adolesc Psychiatry* 2002;41(2):S26–49.

Jadad AR, Boyle M, Cunningham C, Kim M, Schachar R. Treatment of attention-deficit/hyperactivity disorder. *Evid Rep Technol Assess (Summ)* 1999;(11):i–viii, 1–341.

Stiefel G, Besag FM. Cardiovascular effects of methylphenidate, amphetamines, and atomoxetine in the treatment of attention-deficit hyperactivity disorder. *Drug Saf* 2010;33(10):821–42.

Vinson DC. Therapy for attention-deficit hyperactivity disorder. *Arch Fam Med* 1994;3:445–51.

Wender PH, Wolf LE, Wasserstein J. Adults with ADHD. An overview. *Ann N Y Acad Sci* 2001;931:1–16.

THERAPEUTICS

Brands

- Adderall
- Adderall XR
- Evekeo
- Adzenys-XR-ODT
- Dyanavel XR

see index for additional brand names

Generic? Yes **Class**

- Neuroscience-based Nomenclature: dopamine, norepinephrine reuptake inhibitor and releaser (DN-RIRe)
- Stimulant

Commonly Prescribed for

(bold for FDA approved)

- **Attention deficit hyperactivity disorder (ADHD) in children ages 3–12 (Adderall, Evekeo)**
- **Attention deficit hyperactivity disorder (ADHD) in children ages 6–17 (Adderall XR, Evekeo, Dyanavel XR, Adzenys XR-ODT) and in adults (Adderall XR, Evekeo, Adzenys XR-ODT)**
- **Narcolepsy (Adderall, Evekeo)**
- **Exogenous obesity (Evekeo)**
- Treatment-resistant depression

**How the Drug Works**

- ✿ Increases norepinephrine and especially dopamine actions by blocking their reuptake and facilitating their release
- Enhancement of dopamine and norepinephrine actions in certain brain regions (e.g., dorsolateral prefrontal cortex) may improve attention, concentration, executive function, and wakefulness
- Enhancement of dopamine actions in other brain regions (e.g., basal ganglia) may improve hyperactivity
- Enhancement of dopamine and norepinephrine in yet other brain regions (e.g., medial prefrontal cortex, hypothalamus) may improve depression, fatigue, and sleepiness

How Long Until It Works

- Some immediate effects can be seen with first dosing
- Can take several weeks to attain maximum therapeutic benefit

If It Works (for ADHD)

- The goal of treatment of ADHD is reduction of symptoms of inattentiveness, motor hyperactivity, and/or impulsiveness that disrupt social, school, and/or occupational functioning
- Continue treatment until all symptoms are under control or improvement is stable and then continue treatment indefinitely as long as improvement persists
- Reevaluate the need for treatment periodically
- Treatment for ADHD begun in childhood may need to be continued into adolescence and adulthood if continued benefit is documented

If It Doesn't Work (for ADHD)

- Consider adjusting dose or switching to another formulation of d,l-amphetamine or to another agent
- Consider behavioral therapy
- Consider the presence of noncompliance and counsel patient and parents
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., bipolar disorder, substance abuse, medical illness, etc.)

✿ Some ADHD patients and some depressed patients may experience lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require either augmenting with a mood stabilizer or switching to a mood stabilizer

**Best Augmenting Combos for Partial Response or Treatment Resistance**

- Best to attempt other monotherapies prior to augmenting
- For the expert, can combine immediate-release formulation with a sustained-release formulation of d,l-amphetamine for ADHD
- For the expert, can combine with modafinil or atomoxetine for ADHD
- For the expert, can occasionally combine with atypical antipsychotics in highly treatment-resistant cases of bipolar disorder or ADHD
- For the expert, can combine with antidepressants to boost antidepressant efficacy in highly treatment-resistant cases of depression while carefully monitoring patient

Tests

- Before treatment, assess for presence of cardiac disease (history, family history, physical exam)
- Blood pressure should be monitored regularly
- In children, monitor weight and height

SIDE EFFECTS

How Drug Causes Side Effects

- Increases in norepinephrine peripherally can cause autonomic side effects, including tremor, tachycardia, hypertension, and cardiac arrhythmias
- Increases in norepinephrine and dopamine centrally can cause CNS side effects such as insomnia, agitation, psychosis, and substance abuse

Notable Side Effects

- Insomnia, headache, exacerbation of tics, nervousness, irritability, overstimulation, tremor, dizziness
- Anorexia, nausea, dry mouth, constipation, diarrhea, weight loss
- Can temporarily slow normal growth in children (controversial)
- Sexual dysfunction long-term (impotence, libido changes) but can also improve sexual dysfunction short-term



Life-Threatening or Dangerous Side Effects

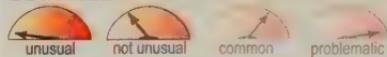
- Psychotic episodes, especially with parenteral abuse
- Seizures
- Palpitations, tachycardia, hypertension
- Rare activation of hypomania, mania, or suicidal ideation (controversial)
- Cardiovascular adverse effects, sudden death in patients with preexisting cardiac structural abnormalities

Weight Gain



- Reported but not expected
- Some patients may experience weight loss

Sedation



- Reported but not expected
- Activation much more common than sedation

What to Do About Side Effects

- Wait
- Adjust dose
- Switch to a long-acting stimulant
- Switch to another agent
- For insomnia, avoid dosing in afternoon/evening

Best Augmenting Agents for Side Effects

- Beta blockers for peripheral autonomic side effects
- Dose reduction or switching to another agent may be more effective since most side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- Narcolepsy: 5–60 mg/day in divided doses
- ADHD: 5–40 mg/day (divided doses for immediate-release tablet, once daily morning dose for extended-release tablet)
- Exogenous obesity: 30 mg/day in divided doses

Dosage Forms

- Immediate-release Adderall tablet 5 mg double-scored, 7.5 mg double-scored, 10 mg double-scored, 12.5 mg double-scored, 15 mg double-scored, 20 mg double-scored, 30 mg double-scored
- Immediate-release Evekeo tablet 5 mg scored, 10 mg double-scored
- Extended-release orally disintegrating tablet (Adzenys XR-ODT) 3.1 mg, 6.3 mg, 9.4 mg, 12.5 mg, 15.7 mg, 18.8 mg
- Extended-release tablet (Adderall XR) 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg
- Extended-release oral suspension (Dynavel XR) 2.5 mg/mL

How to Dose

- Immediate-release Adderall or Evekeo in ADHD (ages 6 and older): initial 5 mg once or twice per day; can increase by 5 mg each week; maximum dose generally 40 mg/day; split daily dose with first dose on waking and every 4–6 hours thereafter
- Immediate-release Evekeo in ADHD (ages 3 to 5): initial 2.5 mg/day; can increase by 2.5 mg each week; administered in divided doses
- Immediate-release Adderall or Evekeo in narcolepsy (ages 12 and older): initial 10 mg/day; can increase by 10 mg each week; split daily dose with first dose on waking and every 4–6 hours thereafter
- Immediate-release Evekeo in narcolepsy (ages 6 to 12): initial 5 mg/day; can increase by 5 mg each week; administered in divided doses
- Extended-release tablet in ADHD: initial 10 mg/day in the morning; can increase by 5–10 mg/day at weekly intervals; maximum dose generally 30 mg/day
- Immediate-release Evekeo in exogenous obesity (ages 12 and older): usual daily dose 30 mg; taken in divided doses of 5–10 mg, 30–60 minutes before meals



Dosing Tips

- Clinical duration of action often differs from pharmacokinetic half-life
- ✿ Immediate-release d,l-amphetamine has 3–6 hour duration of clinical action
- ✿ Extended-release d,l-amphetamine has up to 8-hour duration of clinical action
- Adderall XR is controlled-release and should therefore not be chewed but rather should only be swallowed whole
- Extended-release oral suspension (Dyanavel XR) and extended-release orally disintegrant tablet (Adzenys XR-ODT) should not be substituted for other amphetamine products on a mg-per-mg basis due to differing amphetamine base compositions and pharmacokinetic profiles
- ✿ Controlled-release delivery of d,l-amphetamine is sufficiently long in duration to allow elimination of lunchtime dosing
- ✿ This innovation can be an important practical element in stimulant utilization, eliminating the hassle and pragmatic

difficulties of lunchtime dosing at school, including storage problems, potential diversion, and the need for a medical professional to supervise dosing away from home

- Avoid dosing late in the day because of the risk of insomnia
- May be possible to dose only during the school week for some ADHD patients
- Off-label uses are dosed the same as for ADHD
- ✿ May be able to give drug holidays over the summer in order to reassess therapeutic utility and effects on growth and to allow catch-up from any growth suppression as well as to assess any other side effects and the need to reinstitute stimulant treatment for the next school term
- Side effects are generally dose-related
- Taking with food may delay peak actions for 2–3 hours

Overdose

- Rarely fatal; panic, hyperreflexia, rhabdomyolysis, rapid respiration, confusion, coma, hallucinations, convulsions, arrhythmia, change in blood pressure, circulatory collapse

Long-Term Use

- Often used long-term for ADHD when ongoing monitoring documents continued efficacy
- Dependence and/or abuse may develop
- Tolerance to therapeutic effects may develop in some patients
- Long-term stimulant use may be associated with growth suppression in children (controversial)
- Periodic monitoring of weight, blood pressure, CBC, platelet counts, and liver function may be prudent

Habit Forming

- High abuse potential, Schedule II drug
- Patients may develop tolerance, psychological dependence

How to Stop

- Taper to avoid withdrawal effects
- Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder and may require follow-up and reinstitution of treatment

- Careful supervision is required during withdrawal from abusive use since severe depression may occur

Pharmacokinetics

- Adderall and Adderall XR are a mixture of d-amphetamine and l-amphetamine salts in the ratio of 3:1
- A single dose of Adderall XR 20 mg gives drug levels of both d-amphetamine and l-amphetamine comparable to Adderall immediate-release 20 mg administered in 2 divided doses 4 hours apart
- In adults, half-life for d-amphetamine is 10 hours and for l-amphetamine is 13 hours
- For children ages 6–12, half-life for d-amphetamine is 9 hours and for l-amphetamine is 11 hours



Drug Interactions

- May affect blood pressure and should be used cautiously with agents used to control blood pressure
- Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid, ascorbic acid, fruit juices, etc.) and urinary acidifying agents (ammonium chloride, sodium phosphate, etc.) lower amphetamine plasma levels, so such agents can be useful to administer after an overdose but may also lower therapeutic efficacy of amphetamines
- Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) and urinary alkalinizing agents (acetazolamide, some thiazides) increase amphetamine plasma levels and potentiate amphetamine's actions
- Desipramine and protryptiline can cause striking and sustained increases in brain concentrations of amphetamine and may also add to amphetamine's cardiovascular effects
- Theoretically, other agents with norepinephrine reuptake blocking properties, such as venlafaxine, duloxetine, atomoxetine, milnacipran, and reboxetine, could also add to amphetamine's CNS and cardiovascular effects
- Amphetamines may counteract the sedative effects of antihistamines
- Haloperidol, chlorpromazine, and lithium may inhibit stimulatory effects of amphetamines

- Theoretically, atypical antipsychotics should also inhibit stimulatory effects of amphetamines
- Theoretically, amphetamines could inhibit the antipsychotic actions of antipsychotics
- Theoretically, amphetamines could inhibit the mood-stabilizing actions of atypical antipsychotics in some patients
- Combinations of amphetamines with mood stabilizers (lithium, anticonvulsants, atypical antipsychotics) is generally something for experts only, when monitoring patients closely and when other options fail
- Absorption of phenobarbital, phenytoin, and ethosuximide is delayed by amphetamines
- Amphetamines inhibit adrenergic blockers and enhance adrenergic effects of norepinephrine
- Amphetamines may antagonize hypotensive effects of veratrum alkaloids and other antihypertensives
- Amphetamines increase the analgesic effects of meperidine
- Amphetamines contribute to excessive CNS stimulation if used with large doses of propoxyphene
- Amphetamines can raise plasma corticosteroid levels
- MAOIs slow absorption of amphetamines and thus potentiate their actions, which can cause headache, hypertension, and rarely hypertensive crisis and malignant hyperthermia, sometimes with fatal results
- Use with MAOIs, including within 14 days of MAOI use, is not advised, but this can sometimes be considered by experts who monitor depressed patients closely when other treatment options for depression fail



Other Warnings/ Precautions

- Use with caution in patients with any degree of hypertension, hyperthyroidism, or history of drug abuse
- Children who are not growing or gaining weight should stop treatment, at least temporarily
- May worsen motor and phonic tics

- May worsen symptoms of thought disorder and behavioral disturbance in psychotic patients
- Stimulants have a high potential for abuse and must be used with caution in anyone with a current or past history of substance abuse or alcoholism or in emotionally unstable patients
- Administration of stimulants for prolonged periods of time should be avoided whenever possible or done only with close monitoring, as it may lead to marked tolerance and drug dependence, including psychological dependence with varying degrees of abnormal behavior
- Particular attention should be paid to the possibility of subjects obtaining stimulants for nontherapeutic use or distribution to others and the drugs should in general be prescribed sparingly with documentation of appropriate use
- Usual dosing has been associated with sudden death in children with structural cardiac abnormalities
- Not an appropriate first-line treatment for depression or for normal fatigue
- May lower the seizure threshold
- Emergence or worsening of activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of a mood stabilizer and/or discontinuation of d,l-amphetamine

Do Not Use

- If patient has extreme anxiety or agitation
- If patient has motor tics or Tourette's syndrome or if there is a family history of Tourette's, unless administered by an expert in cases when the potential benefits for ADHD outweigh the risks of worsening tics
- Should generally not be administered with an MAOI, including within 14 days of MAOI use, except in heroic circumstances and by an expert
- If patient has arteriosclerosis, cardiovascular disease, or severe hypertension
- If patient has glaucoma
- If patient has structural cardiac abnormalities
- If there is a proven allergy to any sympathomimetic agent

SPECIAL POPULATIONS

Renal Impairment

- No dose adjustment necessary

Hepatic Impairment

- No dose adjustment necessary

Cardiac Impairment

- Use with caution, particularly in patients with recent myocardial infarction or other conditions that could be negatively affected by increased blood pressure
- Do not use in patients with structural cardiac abnormalities

Elderly

- Some patients may tolerate lower doses better



Children and Adolescents

- Safety and efficacy not established under age 3
- Use in young children should be reserved for the expert
- d,l-amphetamine may worsen symptoms of behavioral disturbance and thought disorder in psychotic children
- d,l-amphetamine has acute effects on growth hormone; long-term effects are unknown but weight and height should be monitored during long-term treatment
- ADHD: ages 3–5: initial 2.5 mg/day; can increase by 2.5 mg each week
- Narcolepsy: ages 6–12: initial 5 mg/day; increase by 5 mg each week
- Sudden death in children and adolescents with serious heart problems has been reported
- American Heart Association recommends EKG prior to initiating stimulant treatment in children, although not all experts agree



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be

phased in gradually for drugs approved on or after June 30, 2001

- Controlled studies have not been conducted in pregnant women
 - Infants whose mothers take d,l-amphetamine during pregnancy may experience withdrawal symptoms
 - In rat and rabbit studies, amphetamine D,L did not affect embryofetal development or survival throughout organogenesis at doses of approximately one and a half and eight times the maximum recommended human dose of 30 mg/day (child)
 - In animal studies, D-amphetamine caused delayed skeletal ossification and decreased post-weaning weight gain in rats; no major malformations occurred in rat or rabbit studies
 - Use in women of childbearing potential requires weighing potential benefits to the mother against potential risks to the fetus
- ✿ For ADHD patients, d,l-amphetamine should generally be discontinued before anticipated pregnancies

Breast Feeding

- Some drug is found in mother's breast milk
- ✿ Recommended either to discontinue drug or bottle feed
- If infant shows signs of irritability, drug may need to be discontinued

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- May work in ADHD patients unresponsive to other stimulants, including pure d-amphetamine sulfate
- New sustained-release option

Potential Disadvantages

- Patients with current or past substance abuse
- Patients with current or past bipolar disorder or psychosis

Primary Target Symptoms

- Concentration, attention span
- Motor hyperactivity
- Impulsiveness
- Physical and mental fatigue
- Daytime sleepiness
- Depression



Pearls

- ✿ May be useful for treatment of depressive symptoms in medically ill elderly patients
- ✿ May be useful for treatment of post-stroke depression
- ✿ A classical augmentation strategy for treatment-refractory depression
- ✿ Specifically, may be useful for treatment of cognitive dysfunction and fatigue as residual symptoms of major depressive disorder unresponsive to multiple prior treatments
- ✿ May also be useful for the treatment of cognitive impairment, depressive symptoms, and severe fatigue in patients with HIV infection and in cancer patients
- Can be used to potentiate opioid analgesia and reduce sedation, particularly in end-of-life management
- ✿ Despite warnings, can be a useful adjunct to MAOIs for heroic treatment of highly refractory mood disorders when monitored with vigilance
- ✿ Can reverse sexual dysfunction caused by psychiatric illness and by some drugs such as SSRIs, including decreased libido, erectile dysfunction, delayed ejaculation, and anorgasmia
- Atypical antipsychotics may be useful in treating stimulant or psychotic consequences of overdose
- Taking with food may delay peak actions for 2–3 hours
- Half-life and duration of clinical action tend to be shorter in younger children
- Drug abuse may actually be lower in ADHD adolescents treated with stimulants than in ADHD adolescents who are not treated
- Some patients respond to or tolerate d,l-amphetamine better than methylphenidate and vice versa

- ✿ Adderall and Adderall XR are a mixture of d-amphetamine and l-amphetamine salts in the ratio of 3:1
- ✿ Specifically, Adderall and Adderall XR combine 1 part dextro-amphetamine saccharate, 1 part dextro-amphetamine sulfate, 1 part d,l-amphetamine aspartate, and 1 part d,l-amphetamine sulfate

- ✿ This mixture of salts may have a different pharmacologic profile, including mechanism of therapeutic action and duration of action, compared to pure dextro-amphetamine, which is given as the sulfate salt
- ✿ Specifically, d-amphetamine may have more profound action on dopamine than norepinephrine whereas l-amphetamine may have a more balanced action on both dopamine and norepinephrine
- ✿ Theoretically, this could lead to relatively more noradrenergic actions of the Adderall

mixture of amphetamine salts than that of pure dextro-amphetamine sulfate, but this is unproven and of no clear clinical significance

- Nevertheless, some patients may respond to or tolerate Adderall/Adderall XR differently than they do pure dextro-amphetamine sulfate
- Adderall XR capsules also contain 2 types of drug-containing beads designed to give a double-pulsed delivery of amphetamines to prolong their release



Suggested Reading

Fry JM. Treatment modalities for narcolepsy. *Neurology* 1998;50(2 Suppl 1):S43–8.

Greenhill LL, Pliszka S, Dulcan MK, et al. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. *J Am Acad Child Adolesc Psychiatry* 2002;41(2 Suppl):S26–49.

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Wender PH, Wolf LE, Wasserstein J. Adults with ADHD. An overview. *Ann NY Acad Sci* 2001;931:1–16.

THERAPEUTICS

Brands

- Abilify
- Abilify Maintena
- Aristada

see index for additional brand names

Generic? Yes**Class**

- Neuroscience-based Nomenclature: dopamine, serotonin receptor partial agonist (DS-RPA)
- Dopamine partial agonist (dopamine stabilizer, atypical antipsychotic, third-generation antipsychotic; sometimes included as a second-generation antipsychotic; also a mood stabilizer)

Commonly Prescribed for

(bold for FDA approved)

- Schizophrenia (ages 13 and older) (**Abilify, Abilify Maintena, Aristada**)
- Maintaining stability in schizophrenia
- Acute mania/mixed mania (ages 10 and older; monotherapy and adjunct)
- Bipolar maintenance (monotherapy and adjunct)
- Depression (adjunct)
- Autism-related irritability in children ages 6 to 17
- Tourette's disorder in children ages 6 to 18
- Acute agitation associated with schizophrenia or bipolar disorder (IM)
- Bipolar depression
- Other psychotic disorders
- Behavioral disturbances in dementias
- Behavioral disturbances in children and adolescents
- Disorders associated with problems with impulse control

**How the Drug Works**

- Partial agonism at dopamine 2 receptors
- Theoretically reduces dopamine output when dopamine concentrations are high, thus improving positive symptoms and mediating antipsychotic actions
- Theoretically increases dopamine output when dopamine concentrations are low, thus improving cognitive, negative, and mood symptoms

- Actions at dopamine 3 receptors could theoretically contribute to aripiprazole's efficacy
- Partial agonism at 5HT1A receptors may be relevant at clinical doses
- Blockade of serotonin type 2A receptors may contribute at clinical doses to cause enhancement of dopamine release in certain brain regions, thus reducing motor side effects and possibly improving cognitive and affective symptoms
- Blockade of serotonin type 2C and 7 receptors as well as partial agonist actions at 5HT1A receptors may contribute to antidepressant actions

How Long Until It Works

- Psychotic and manic symptoms can improve within 1 week, but it may take several weeks for full effect on behavior as well as on cognition and affective stabilization
- Classically recommended to wait at least 4–6 weeks to determine efficacy of drug, but in practice some patients require up to 16–20 weeks to show a good response, especially on cognitive symptoms

If It Works

- Most often reduces positive symptoms in schizophrenia but does not eliminate them
- Can improve negative symptoms, as well as aggressive, cognitive, and affective symptoms in schizophrenia
- Most schizophrenic patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third
- Perhaps 5–15% of schizophrenic patients can experience an overall improvement of greater than 50–60%, especially when receiving stable treatment for more than a year
- Such patients are considered super-responders or "awakeners" since they may be well enough to be employed, live independently, and sustain long-term relationships
- Many bipolar patients may experience a reduction of symptoms by half or more
- Continue treatment until reaching a plateau of improvement
- After reaching a satisfactory plateau, continue treatment for at least a year after first episode of psychosis

- For second and subsequent episodes of psychosis, treatment may need to be indefinite
- Even for first episodes of psychosis, it may be preferable to continue treatment indefinitely to avoid subsequent episodes
- Treatment may not only reduce mania but also prevent recurrences of mania in bipolar disorder

If It Doesn't Work

- Try one of the other atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, paliperidone, amisulpride, asenapine, iloperidone, lurasidone)
- If two or more antipsychotic monotherapies do not work, consider clozapine
- Some patients may require treatment with a conventional antipsychotic
- If no first-line atypical antipsychotic is effective, consider higher doses or augmentation with valproate or lamotrigine
- Consider noncompliance and switch to another antipsychotic with fewer side effects or to an antipsychotic that can be given by depot injection
- Consider initiating rehabilitation and psychotherapy such as cognitive remediation
- Consider presence of concomitant drug abuse



Best Augmenting Combos for Partial Response or Treatment Resistance

- Valproic acid (valproate, divalproex, divalproex ER)
- Other mood-stabilizing anticonvulsants (carbamazepine, oxcarbazepine, lamotrigine)
- Lithium
- Benzodiazepines

Tests

Before starting an atypical antipsychotic

- Weigh all patients and track BMI during treatment
- Get baseline personal and family history of diabetes, obesity, dyslipidemia, hypertension, and cardiovascular disease
- Get waist circumference (at umbilicus), blood pressure, fasting plasma glucose, and fasting lipid profile
- Determine if the patient is
- overweight (BMI 25.0–29.9)
- obese (BMI ≥30)
- has pre-diabetes (fasting plasma glucose 100–125 mg/dL)
- has diabetes (fasting plasma glucose >126 mg/dL)
- has hypertension (BP >140/90 mm Hg)
- has dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol)

- Treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management

Monitoring after starting an atypical antipsychotic

- BMI monthly for 3 months, then quarterly
- Consider monitoring fasting triglycerides monthly for several months in patients at high risk for metabolic complications and when initiating or switching antipsychotics
- Blood pressure, fasting plasma glucose, fasting lipids within 3 months and then annually, but earlier and more frequently for patients with diabetes or who have gained >5% of initial weight
- Treat or refer for treatment and consider switching to another atypical antipsychotic for patients who become overweight, obese, pre-diabetic, diabetic, hypertensive, or dyslipidemic while receiving an atypical antipsychotic
- Even in patients without known diabetes, be vigilant for the rare but life-threatening onset of diabetic ketoacidosis, which always requires immediate treatment, by monitoring for the rapid onset of polyuria, polydipsia, weight loss, nausea, vomiting, dehydration, rapid respiration, weakness and clouding of sensorium, even coma
- Patients with low white blood cell count (WBC) or history of drug-induced leucopenia/neutropenia should have complete blood count (CBC) monitored frequently during the first few months and aripiprazole should be discontinued at the first sign of decline of WBC in the absence of other causative factors

SIDE EFFECTS

How Drug Causes Side Effects

- By blocking alpha 1 adrenergic receptors, it can cause dizziness, sedation, and hypotension
- Partial agonist actions at dopamine 2 receptors in the striatum can cause motor side effects, such as akathisia
- Partial agonist actions at dopamine 2 receptors can also cause nausea, occasional vomiting, and activating side effects
- Mechanism of any possible weight gain is unknown; weight gain is not common with aripiprazole and may thus have a different mechanism from atypical antipsychotics for which weight gain is common or problematic
- Mechanism of any possible increased incidence of diabetes or dyslipidemia is unknown; early experience suggests these complications are not clearly associated with aripiprazole and if present may therefore have a different mechanism from that of atypical antipsychotics associated with an increased incidence of diabetes and dyslipidemia

Notable Side Effects

- Dizziness, insomnia, akathisia, activation
- Nausea, vomiting
- Orthostatic hypotension, occasionally during initial dosing
- Constipation
- Headache, asthenia, sedation
- Theoretical risk of tardive dyskinesia



Life-Threatening or Dangerous Side Effects

- Rare impulse control problems
- Rare neuroleptic malignant syndrome (much reduced risk compared to conventional antipsychotics)
- Rare seizures
- Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis

Weight Gain



- Reported in a few patients, especially those with low BMIs, but not expected

- Less frequent and less severe than for most other antipsychotics
- May be more risk of weight gain in children than in adults

Sedation



- Reported in a few patients but not expected
- May be less than for some other antipsychotics, but never say never
- Can be activating

What to Do About Side Effects

- Wait
- Wait
- Wait
- Reduce the dose
- Anticholinergics or a low dose benzodiazepine or a beta blocker may reduce akathisia when present
- Weight loss, exercise programs, and medical management for high BMIs, diabetes, dyslipidemia
- Switch to another atypical antipsychotic

Best Augmenting Agents for Side Effects

- Benztrapine or trihexyphenidyl for motor side effects and akathisia
- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 15–30 mg/day for schizophrenia and mania
- 2–10 mg/day for augmenting SSRIs/SNRIs in depression
- 5–15 mg/day for autism
- 5–20 mg/day for Tourette's disorder
- 300–400 mg/4 weeks (LAI Maintena; see Aripiprazole Depot Formulations after Pearls for dosing and use)
- 441 mg, 662 mg, or 882 mg administered monthly or 882 mg administered every 6 weeks (LAI Aristada; see Aripiprazole Depot Formulations after Pearls for dosing and use)

Dosage Forms

- Tablet 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg
- Orally disintegrating tablet 10 mg, 15 mg

- Oral solution 1 mg/mL
- Injection 9.75 mg/1.3 mL
- Depot (Maintena) 300 mg, 400 mg
- Depot (Aristada) 441 mg, 662 mg, 882 mg

How to Dose – Oral and Acute IM

- Schizophrenia, mania: initial approved recommendation is 10–15 mg/day; maximum approved dose 30 mg/day
- Depression (adjunct): initial dose 2–5 mg/day; can increase by 5 mg/day at intervals of no less than 1 week; maximum dose 15 mg/day
- Autism: initial dose 2 mg/day; can increase by 5 mg/day at intervals of no less than 1 week; maximum dose 15 mg/day
- Tourette's disorder (patients weighing less than 50 kg): initial dose 2 mg/day; after 2 days increase to 5 mg/day; after 1 additional week can increase to 10 mg/day if needed
- Tourette's disorder (patients weighing more than 50 kg): initial dose 2 mg/day; after 2 days increase to 5 mg/day; after 5 additional days can increase to 10 mg/day; can increase by 5 mg/day at intervals of no less than 1 week; maximum dose 20 mg/day
- Agitation: 9.75 mg/1.3 ml; maximum 30 mg/day
- Depot: must initiate oral aripiprazole first; after tolerability is established can administer initial injection along with an overlapping 14-day (Maintena) or 21-day (Aristada) dosing of oral aripiprazole; initial and maintenance doses are described under dosing tips below
- Oral solution: solution doses can be substituted for tablet doses on a mg-per-mg basis up to 25 mg; patients receiving 30-mg tablet should receive 25-mg solution



Dosing Tips – Oral

- For some, less may be more: frequently, patients not acutely psychotic may need to be dosed lower (e.g., 2.5–10 mg/day) in order to avoid akathisia and activation and for maximum tolerability
- For others, more may be more: rarely, patients may need to be dosed higher than 30 mg/day for optimum efficacy
- Consider administering 1–5 mg as the oral solution for children and adolescents, as

well as for adults very sensitive to side effects

- Although studies suggest patients switching to aripiprazole from another antipsychotic can do well with rapid switch or with cross-titration, clinical experience suggests many patients may do best by adding either an intermediate or full dose of aripiprazole to the maintenance dose of the first antipsychotic for at least several days and possibly as long as 3 or 4 weeks prior to slow down-titration of the first antipsychotic. See also the Switching section below, after Pearls
- Rather than raise the dose above these levels in acutely agitated patients requiring acute antipsychotic actions, consider augmentation with a benzodiazepine or conventional antipsychotic, either orally or intramuscularly
- Rather than raise the dose above these levels in partial responders, consider augmentation with a mood-stabilizing anticonvulsant, such as valproate or lamotrigine
- Children and elderly should generally be dosed at the lower end of the dosage spectrum
- Due to its very long half-life, aripiprazole will take longer to reach steady state when initiating dosing, and longer to wash out when stopping dosing, than other atypical antipsychotics
- Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³

Overdose

- No fatalities have been reported; sedation, vomiting

Long-Term Use

- Approved to delay relapse in long-term treatment of schizophrenia
- Approved for long-term maintenance in bipolar disorder
- Often used for long-term maintenance in various behavioral disorders

Habit Forming

- No

How to Stop

- See Switching section of individual agents for how to stop aripiprazole

- Rapid discontinuation could theoretically lead to rebound psychosis and worsening of symptoms, but less likely with aripiprazole due to its long half-life

Pharmacokinetics

- Metabolized primarily by CYP450 2D6 and CYP450 3A4
- Mean elimination half-life 75 hours (aripiprazole) and 94 hours (major metabolite dehydro-aripiprazole)
- Food does not affect absorption



Drug Interactions

- Ketaconazole and possibly other CYP450 3A4 inhibitors such as nefazodone, fluvoxamine, and fluoxetine may increase plasma levels of aripiprazole
- Carbamazepine and possibly other inducers of CYP450 3A4 may decrease plasma levels of aripiprazole
- Quinidine and possibly other inhibitors of CYP450 2D6 such as paroxetine, fluoxetine, and duloxetine may increase plasma levels of aripiprazole
- Aripiprazole may enhance the effects of antihypertensive drugs
- Aripiprazole may antagonize levodopa, dopamine agonists



Other Warnings/ Precautions

- There have been reports of problems with impulse control in patients taking aripiprazole, including compulsive gambling, shopping, binge eating, and sexual activity; use caution when prescribing to patients at high risk for impulse-control problems (e.g., patients with bipolar disorder, impulsive personality, obsessive-compulsive disorder, substance use disorders) and monitor all patients for emergence of these symptoms; dose should be lowered or discontinued if impulse-control problems manifest
- Use with caution in patients with conditions that predispose to hypotension (dehydration, overheating)
- Dysphagia has been associated with antipsychotic use, and aripiprazole should be used cautiously in patients at risk for aspiration pneumonia

Do Not Use

- If there is a proven allergy to aripiprazole

SPECIAL POPULATIONS

Renal Impairment

- Dose adjustment not necessary

Hepatic Impairment

- Dose adjustment not necessary

Cardiac Impairment

- Use in patients with cardiac impairment has not been studied, so use with caution because of risk of orthostatic hypotension

Elderly

- Dose adjustment generally not necessary, but some elderly patients may tolerate lower doses better
- Although atypical antipsychotics are commonly used for behavioral disturbances in dementia, no agent has been approved for treatment of elderly patients with dementia-related psychosis
- Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo, and also have an increased risk of cerebrovascular events



Children and Adolescents

- Approved for use in schizophrenia (ages 13 and older), manic/mixed episodes (ages 10 and older), irritability associated with autism (ages 6–17), and treatment of Tourette's disorder (ages 6–18)
- Clinical experience and early data suggest aripiprazole may be safe and effective for behavioral disturbances in children and adolescents, especially at lower doses
- Children and adolescents using aripiprazole may need to be monitored more often than adults and may tolerate lower doses better
- May be more risk of weight gain in children than in adults



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- There is a risk of abnormal muscle movements and withdrawal symptoms in newborns whose mothers took an antipsychotic during the third trimester; symptoms may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty feeding
- In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects, at doses higher than the maximum recommended human dose
- Psychotic symptoms may worsen during pregnancy and some form of treatment may be necessary
- Aripiprazole may be preferable to anticonvulsant mood stabilizers if treatment is required during pregnancy
- National Pregnancy Registry for Atypical Antipsychotics: 1-866-961-2388 or <http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/>

Breast Feeding

- Some drug is found in mother's breast milk
- Recommended either to discontinue drug or bottle feed
- Infants of women who choose to breast feed while on aripiprazole should be monitored for possible adverse effects

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Some cases of psychosis and bipolar disorder refractory to treatment with other antipsychotics

- Patients concerned about gaining weight and patients who are already obese or overweight
- Patients with diabetes
- Patients with dyslipidemia (especially elevated triglycerides)
- Patients requiring rapid onset of antipsychotic action without dosage titration
- Patients who wish to avoid sedation

Potential Disadvantages

- Patients in whom sedation is desired
- May be more difficult to dose for children, elderly, or "off-label" uses

Primary Target Symptoms

- Positive symptoms of psychosis
- Negative symptoms of psychosis
- Cognitive symptoms
- Unstable mood and depression
- Aggressive symptoms



Pearls

- Approved as an adjunct treatment for depression (e.g., to SSRIs, SNRIs)
- May work better in 2–10 mg/day range than at higher doses for augmenting SSRIs/SNRIs in treatment-resistant unipolar depression
- Frequently used for bipolar depression as augmenting agent to lithium, valproate and/or lamotrigine
- Well accepted in clinical practice when wanting to avoid weight gain because less weight gain than most other antipsychotics
- Well accepted in clinical practice when wanting to avoid sedation because less sedation than most other antipsychotics at all doses
- Can even be activating, which can be reduced by lowering the dose or starting at a lower dose
- If sedation is desired, a benzodiazepine can be added short-term at the initiation of treatment until symptoms of agitation and insomnia are stabilized or intermittently as needed
- May not have diabetes or dyslipidemia risk, but monitoring is still indicated
- Anecdotal reports of utility in treatment-resistant cases of psychosis

- Has a very favorable tolerability profile in clinical practice
- Favorable tolerability profile leading to “off-label” uses for many indications other than schizophrenia (e.g., bipolar II disorder, including hypomanic, mixed, rapid cycling, and depressed phases; treatment-resistant depression; anxiety disorders)
- A short-acting intramuscular formulation is available as well as long-acting depot
- Lacks D1 antagonist, anticholinergic, and antihistamine properties, which may explain relative lack of sedation or cognitive side effects in most patients
- High affinity of aripiprazole for D2 receptors means that combining with other D2 antagonist antipsychotics could reverse their actions and thus often makes sense not to combine with other antipsychotics
- An exception to this is in case of hyperprolactinemia or galactorrhea, when administration of even low dose (1–5 mg) can reverse the hyperprolactinemia/galactorrhea of other antipsychotics, also proving that aripiprazole interferes with the D2 actions of other antipsychotics
- Ability of Maintena (depot) may be particularly well suited to early-onset psychosis/first-episode psychosis to reduce rehospitalizations and to enhance adherence with relatively low side effect burden

DEPOT FORMULATIONS

	Monohydrate (Maintena)	Lauroxil (Aristada)
Vehicle	Water	Water
Tmax	6.5–7.1 days	44.1–50.0 days
T1/2 with multiple dosing	29.9–46.5 days	29.2–34.9 days
Time to reach steady state		4 monthly injections
Able to be loaded	No	No
Dosing schedule (maintenance)	4 weeks	4–6 weeks
Injection site	Intramuscular gluteal	Intramuscular injection in deltoid (441 mg dose only) or gluteal (441, 662, or 882 mg)
Needle gauge	21	20 or 21
Dosage forms	300 mg, 400 mg	441 mg, 662 mg, 882 mg
Injection volume	200 mg/mL; range 0.8 mL (160 mg)–2 mL (400 mg)	441 mg/1.6 mL; 662 mg/2.4 mL; 882 mg/3.2 mL

Usual Dosage Range

- 300–400 mg/4 weeks (monohydrate Maintena)
- 441 mg, 662 mg, or 882 mg administered monthly or 882 mg administered every 6 weeks (lauroxil Aristada)

How to Dose

- Not recommended for patients who have not first demonstrated tolerability to oral aripiprazole (in clinical trials, 2 oral or short-acting IM doses are generally used to establish tolerability)

- Loading is not possible, necessitating oral coverage for 14 days (Maintena) or 21 days (Aristada)
- Conversion from oral to Maintena: administer initial 400 mg injection along with an overlapping 14-day dosing of oral aripiprazole
- Conversion from oral to Aristada: administer initial injection (441 mg, 662 mg, or 882 mg) along with an overlapping 21-day dosing of oral aripiprazole

Dosing Tips

- With LAIs, the absorption rate constant is slower than the elimination rate constant, thus resulting in “flip-flop” kinetics—i.e., time to steady-state is a function of absorption rate, while concentration at steady-state is a function of elimination rate
- The rate-limiting step for plasma drug levels for LAIs is not drug metabolism, but rather slow absorption from the injection site
- In general, 5 half-lives of any medication are needed to achieve 97% of steady-state levels
- The long half-lives of depot antipsychotics mean that one must either adequately load the dose (if possible) or provide oral supplementation
- The failure to adequately load the dose leads either to prolonged cross-titration from oral antipsychotic or to sub-therapeutic antipsychotic plasma

levels for weeks or months in patients who are not receiving (or adhering to) oral supplementation

- Because plasma antipsychotic levels increase gradually over time, dose requirements may ultimately decrease from initial; obtaining periodic plasma levels can be beneficial to prevent unnecessary plasma level creep
- The time to get a blood level for patients receiving LAI is the morning of the day they will receive their next injection
- Advantages: refrigeration not required; option of 6-week injections with Aristada
- Disadvantages: both formulations require oral coverage
- Downward dose adjustment is needed for poor CYP450 2D6 metabolizers and patients taking strong CYP450 2D6 or 3A4 inhibitors; avoid use with strong CYP450 3A4 inducers, as this can lead to sub-therapeutic plasma levels

Maintena

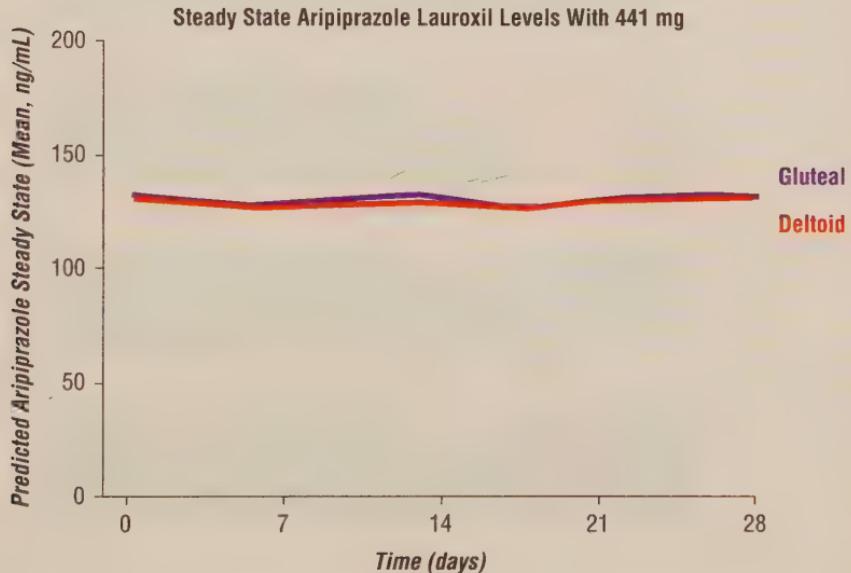
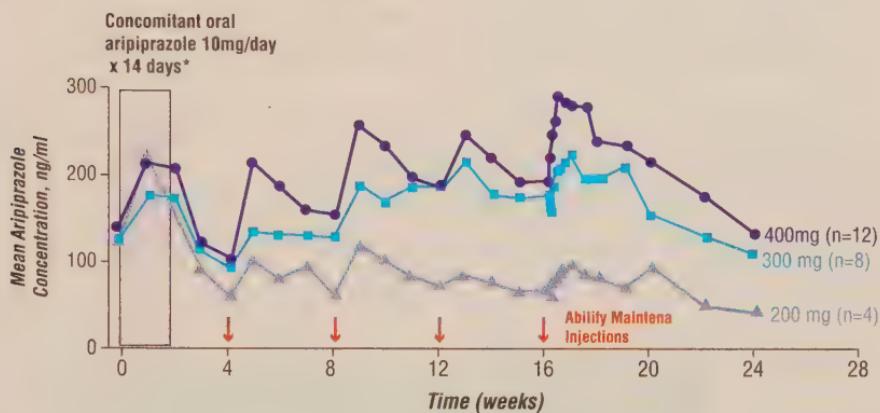
	Adjusted dose for patients taking 400 mg	Adjusted dose for patients taking 300 mg
Poor 2D6 metabolizers	300 mg	N/A
Patients taking strong 2D6 OR 3A4 inhibitors	300 mg	200 mg
Poor 2D6 metabolizers taking concomitant 3A4 inhibitors	200 mg	N/A
Patients taking 2D6 AND 3A4 inhibitors	200 mg	160 mg
Patients taking 3A4 inducers	Avoid	Avoid

Aristada

	Adjusted dose for patients taking 441 mg	Adjusted dose for patients taking 662 mg	Adjusted dose for patients taking 882 mg
Poor 2D6 metabolizers	N/A	N/A	N/A
Patients taking strong 2D6 OR 3A4 inhibitors	N/A	441 mg	662 mg
Poor 2D6 metabolizers taking concomitant 3A4 inhibitors	N/A	441 mg	441 mg
Patients taking 2D6 AND 3A4 inhibitors	N/A	Avoid	Avoid
Patients taking 3A4 inducers	662 mg	N/A	N/A

Switching from Oral Antipsychotics to Aripiprazole Depot Formulations

Aripiprazole Monohydrate Kinetics

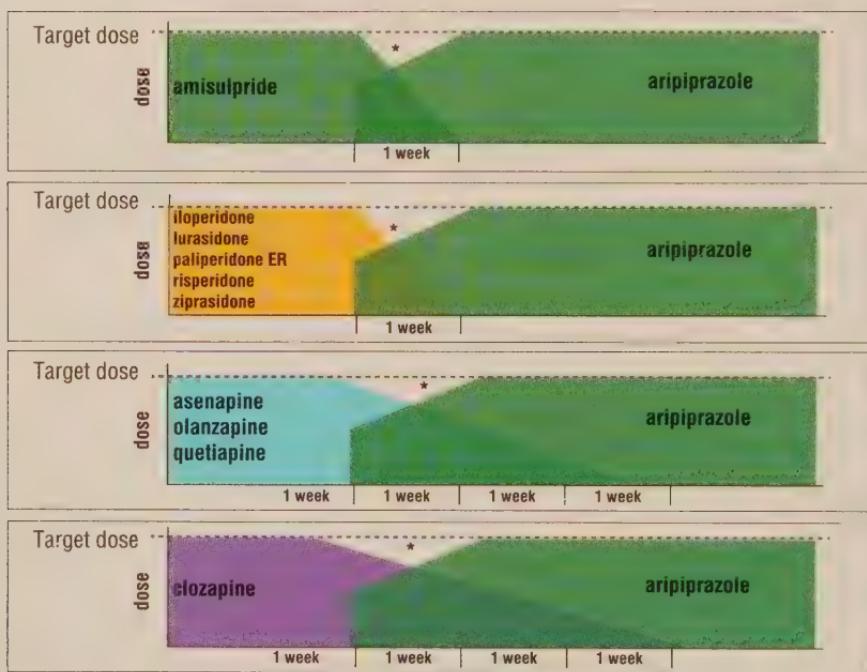


- Discontinuation of oral antipsychotic can begin following oral coverage of 14 days (Maintena) or 21 days (Aristada)
- How to discontinue oral formulations
 - Down-titration is not required for: amisulpride, aripiprazole, brexpiprazole, cariprazine, paliperidone ER
 - 1-week down-titration is required for: iloperidone, lurasidone, risperidone, ziprasidone
 - 3–4-week down-titration is required for: asenapine, olanzapine, quetiapine
 - 4+ week down-titration is required for: clozapine
 - For patients taking benzodiazepine or anticholinergic medication, this can be continued during cross-titration to help alleviate side effects such as insomnia, agitation, and/or psychosis. Once the patient is stable on LAI, these can be tapered one at a time as appropriate.

THE ART OF SWITCHING

**Switching from Oral Antipsychotics to Aripiprazole**

- It is advisable to begin aripiprazole at an intermediate dose and build the dose rapidly over 3–7 days
- Clinical experience has shown that asenapine, quetiapine, and olanzapine should be tapered off slowly over a period of 3–4 weeks, to allow patients to readapt to the withdrawal of blocking cholinergic, histaminergic, and alpha-1 receptors
- Clozapine should always be tapered off slowly, over a period of 4 weeks or more
- * Benzodiazepine or anticholinergic medication can be administered during cross-titration to help alleviate side effects such as insomnia, agitation, and/or psychosis





Suggested Reading

Andrezina R, Josiassen RC, Marcus RN, et al. Intramuscular aripiprazole for the treatment of acute agitation in patients with schizophrenia or schizoaffective disorder: a double-blind, placebo-controlled comparison with intramuscular haloperidol. *Psychopharmacology* 2006;188(3):281–92.

Citrome L. Adjunctive aripiprazole, olanzapine, or quetiapine for major depressive disorder: an analysis of number needed to treat, number needed to harm, and likelihood to be helped or harmed. *Postgrad Med* 2010;122(4):39–48.

El-Sayeh HG, Morganti C. Aripiprazole for schizophrenia. *Cochrane Database Syst Rev* 2006;2:CD004578.

Kane JM, Sanchez R, Perry PP, et al. Aripiprazole intramuscular depot as maintenance treatment in patients with

schizophrenia: a 52-week, multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2012;73(5):617–24.

Marcus RN, McQuade RD, Carson WH, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol* 2008;28(2):156–65.

Nasrallah HA. Atypical antipsychotic-induced metabolic side effects: insights from receptor-binding profiles. *Mol Psychiatry* 2008;13(1):27–35.

Smith LA, Cornelius V, Warnock A, Tacchi MJ, Taylor D. Pharmacological interventions for acute bipolar mania: a systematic review of randomized placebo-controlled trials. *Bipolar Disord* 2007;9(6):551–60.

THERAPEUTICS

Brands • Nuvigil*see index for additional brand names***Generic?** Yes**Class**

- Neuroscience-based Nomenclature: dopamine reuptake inhibitor (D-RI)
- Wake-promoting

Commonly Prescribed for*(bold for FDA approved)*

- Reducing excessive sleepiness in patients with narcolepsy and shift work sleep disorder
- Reducing excessive sleepiness in patients with obstructive sleep apnea/hypopnea syndrome (OSAHS) (adjunct to standard treatment for underlying airway obstruction)
- Attention deficit hyperactivity disorder (ADHD)
- Fatigue and sleepiness in depression
- Fatigue in multiple sclerosis
- Bipolar depression

**How the Drug Works**

- Unknown, but clearly different from classical stimulants such as methylphenidate and amphetamine
- Binds to and requires the presence of the dopamine transporter; also requires the presence of alpha adrenergic receptors
- Hypothetically acts as an inhibitor of the dopamine transporter
- Increases neuronal activity selectively in the hypothalamus
- Presumably enhances activity in hypothalamic wakefulness center (TMN, tuberomammillary nucleus) within the hypothalamic sleep-wake switch by an unknown mechanism
- Activates tuberomammillary nucleus neurons that release histamine
- Activates other hypothalamic neurons that release orexin/hypocretin

How Long Until It Works

- Can immediately reduce daytime sleepiness and improve cognitive task performance within 2 hours of first dosing

- Can take several days to optimize dosing and clinical improvement

If It Works

- Improves daytime sleepiness and may improve attention as well as fatigue
- Does not generally prevent one from falling asleep when needed
- May not completely normalize wakefulness
- Treat until improvement stabilizes and then continue treatment indefinitely as long as improvement persists (studies support at least 12 weeks of treatment)

If It Doesn't Work

- Change dose; some patients may do better with an increased dose but some may actually do better with a decreased dose
- Augment or consider an alternative treatment for daytime sleepiness, fatigue, or ADHD

**Best Augmenting Combos for Partial Response or Treatment Resistance**

- Armodafinil is itself an adjunct to standard treatments for OSAHS; if continuous positive airway pressure (CPAP) is the treatment of choice, a maximal effort to treat first with CPAP should be made prior to initiating armodafinil and CPAP should be continued after initiation of armodafinil
- Armodafinil is itself an augmenting therapy to antidepressants for residual sleepiness and fatigue in major depressive disorder
- Armodafinil is itself an augmenting therapy to mood stabilizers for bipolar depression
- Best to attempt another monotherapy prior to augmenting with other drugs in the treatment of sleepiness associated with sleep disorders or problems concentrating in ADHD
- Combination of armodafinil with stimulants such as methylphenidate or amphetamine or with atomoxetine for ADHD has not been systematically studied
- However, such combinations may be useful options for experts, with close monitoring, when numerous monotherapies for sleepiness or ADHD have failed

Tests

- None for healthy individuals

SIDE EFFECTS

How Drug Causes Side Effects

- Unknown
- CNS side effects presumably due to excessive CNS actions on various neurotransmitter systems

Notable Side Effects

- ✖ Headache
- Anxiety, dizziness, insomnia
- Dry mouth, diarrhea, nausea



Life-Threatening or Dangerous Side Effects

- Transient EKG ischemic changes in patients with mitral valve prolapse or left ventricular hypertrophy have been reported (rare)
- Rare activation of (hypo)mania, anxiety, hallucinations, or suicidal ideation
- Rare severe dermatologic reactions (Stevens-Johnson syndrome and others)
- Angioedema, anaphylactoid reactions, and multi-organ hypersensitivity reactions have been reported

Weight Gain



- Reported but not expected

Sedation



- Reported but not expected
- Patients are usually awakened and some may be activated

What to Do About Side Effects

- Wait
- Lower the dose
- For activation or insomnia, do not give in the evening
- If unacceptable side effects persist, discontinue use
- For life-threatening or dangerous side effects, discontinue immediately (e.g., at first sign of a drug-related rash)

Best Augmenting Agents for Side Effects

- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 150–250 mg/day

Dosage Forms

- Tablet 50 mg, 150 mg, 250 mg

How to Dose

- Titration up or down only necessary if not optimally efficacious at the standard starting dose of 150 mg once a day
- For OSA and narcolepsy, give as a single dose in the morning
- For shift work sleep disorder, give as a single dose 1 hour prior to the start of the work shift



Dosing Tips

✖ For sleepiness, more may be more: higher doses may be better than lower doses in patients with daytime sleepiness in sleep disorders

✖ For problems concentrating and fatigue, less may be more: lower doses may be paradoxically better than higher in some patients

• At high doses, may slightly induce its own metabolism, possibly by actions of inducing CYP450 3A4

• Dose may creep upward in some patients with long-term treatment due to autoinduction; drug holiday may restore efficacy at original dose

• Pharmacokinetics and clinical experience suggest armodafinil has longer duration of action than racemic modafinil, generally requiring only once daily administration

Overdose

- Agitation, insomnia, increase in hemodynamic parameters
- Postmarketing experience includes CNS symptoms, such as restlessness, disorientation, confusion, excitation, and hallucinations; digestive changes, such as

nausea and diarrhea; and cardiovascular changes, such as tachycardia, bradycardia, hypertension, and chest pain

Long-Term Use

- The need for continued treatment should be reevaluated periodically.

Habit Forming

- Schedule IV; may have some potential for abuse but unusual in clinical practice

How to Stop

- Taper not necessary; patients may have sleepiness on discontinuation

Pharmacokinetics

- Metabolized by the liver
- Elimination half-life approximately 15 hours
- Inhibits CYP450 2C19
- Induces CYP450 3A4 (and slightly 1A2)



Drug Interactions

- May increase plasma levels of drugs metabolized by CYP450 2C19 (e.g., diazepam, phenytoin, propranolol)
- May decrease plasma levels of CYP450 3A4 substrates such as ethinyl estradiol and triazolam
- Due to induction of CYP450 3A4, effectiveness of steroid contraceptives may be reduced by armodafinil, including 1 month after discontinuation
- Inducers or inhibitors of CYP450 3A4 may affect levels of armodafinil (e.g., carbamazepine may lower modafinil plasma levels; fluvoxamine and fluoxetine may raise armodafinil plasma levels)
- Armodafinil may slightly reduce its own levels by autoinduction of CYP450 3A4
- Patients on armodafinil and warfarin should have prothrombin times monitored
- Methylphenidate and dextroamphetamine may delay absorption of armodafinil by an hour
- However, coadministration with methylphenidate or dextroamphetamine does not significantly change the pharmacokinetics of armodafinil or either stimulant
- Interaction studies with MAOIs have not been performed, but MAOIs can be given with armodafinil by experts with cautious monitoring



Other Warnings/ Precautions

- Patients with history of drug abuse should be monitored closely
- Armodafinil may cause CNS effects similar to those caused by other CNS agents (e.g., changes in mood and, theoretically, activation of psychosis, mania, or suicidal ideation)
- Armodafinil should be used in patients with sleep disorders that have been completely evaluated for narcolepsy, OSAHS, and shift work sleep disorder
- In OSAHS patients for whom CPAP is the treatment of choice, a maximal effort to treat first with CPAP should be made prior to initiating armodafinil, and then CPAP should be continued after initiating armodafinil
- The effectiveness of steroid contraceptives may be reduced when used with armodafinil and for 1 month after discontinuation of armodafinil
- Armodafinil is not a replacement for sleep

Do Not Use

- If there is a proven allergy to armodafinil or modafinil

SPECIAL POPULATIONS

Renal Impairment

- Use with caution

Hepatic Impairment

- Reduce dose in severely impaired patients

Cardiac Impairment

- Use with caution
- Not recommended for use in patients with a history of left ventricular hypertrophy, ischemic EKG changes, chest pain, arrhythmias, or recent myocardial infarction

Elderly

- Limited experience in patients over 65
- Clearance of armodafinil may be reduced in elderly patients



Children and Adolescents

- Safety and efficacy have not been established
- Can be used cautiously by experts for children and adolescents



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Intrauterine growth restriction and spontaneous abortion have been reported with armodafinil and modafinil
- In animal studies, developmental toxicity was observed at clinically relevant plasma exposures
- Use in women of childbearing potential requires weighing potential benefits to the mother against potential risks to the fetus
- Generally, armodafinil should be discontinued prior to anticipated pregnancies

Breast Feeding

- Unknown if armodafinil is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- Recommended either to discontinue drug or bottle feed

Potential Disadvantages

- May not work as well as stimulants in some patients

Primary Target Symptoms

- Sleepiness
- Concentration
- Physical and mental fatigue



Pearls

- Armodafinil is the longer-lasting R enantiomer of racemic modafinil
- Armodafinil maintains high plasma concentrations later in the day than does modafinil on a mg-to-mg basis, which could theoretically result in improved wakefulness throughout the day with armodafinil compared to modafinil
- Armodafinil is not a replacement for sleep
- The treatment for sleep deprivation is sleep, not armodafinil
- Controlled studies suggest armodafinil improves attention in OSAHS and shift work sleep disorder, but controlled studies of attention have not been performed in ADHD or major depressive disorder
- Controlled studies of racemic modafinil in ADHD suggest improvement in attention
- May be useful to treat fatigue in patients with depression as well as other disorders, such as multiple sclerosis, myotonic dystrophy, HIV/AIDS
- May be useful in treating sleepiness associated with opioid analgesia, particularly in end-of-life management
- Subjective sensation associated with armodafinil is usually one of normal wakefulness, not of stimulation, although jitteriness can rarely occur
- Compared to traditional stimulants, armodafinil has a novel mechanism of action, novel therapeutic uses, and less abuse potential
- Alpha 1 antagonists such as prazosin may block the therapeutic actions of armodafinil
- Some controlled trials suggest efficacy in bipolar depression as an adjunct to atypical antipsychotics

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Selective for areas of brain involved in sleep/wake promotion
- Less activating and less abuse potential than stimulants



Suggested Reading

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medications metabolized by cytochrome P450 enzymes 1A2, 3A4, and 2C19 in healthy subjects. *Clin Pharmacokinet* 2008;47(1): 61–74.

Garnock-Jones KP, Dhillon S, Scott LJ. Armodafinil. *CNS Drugs* 2009;23(9):793–803.

THERAPEUTICS

Brands • SAPHRIS

see index for additional brand names

Generic? No



Class

- Neuroscience-based Nomenclature: dopamine, serotonin, norepinephrine receptor antagonist (DSN-RAn)
- Atypical antipsychotic (serotonin-dopamine antagonist; second generation antipsychotics; also a mood stabilizer)

Commonly Prescribed for

(bold for FDA approved)

- **Schizophrenia, acute and maintenance (adults)**
- **Acute mania/mixed mania, monotherapy (ages 10 to 17 and in adults)**
- **Acute mania/mixed mania, adjunct to lithium or valproate (adults)**
- Other psychotic disorders
- Bipolar maintenance
- Bipolar depression
- Treatment-resistant depression
- Behavioral disturbances in dementia
- Behavioral disturbances in children and adolescents
- Disorders associated with problems with impulse control



How the Drug Works

- Blocks dopamine 2 receptors, reducing positive symptoms of psychosis and stabilizing affective symptoms
- Blocks serotonin 2A receptors, causing enhancement of dopamine release in certain brain regions and thus reducing motor side effects and possibly improving cognitive and affective symptoms
- Serotonin 2C, serotonin 7, and alpha 2 antagonist properties may contribute to antidepressant actions

How Long Until It Works

- Psychotic symptoms can improve within 1 week, but it may take several weeks for full effect on behavior as well as on cognition
- Classically recommended to wait at least 4–6 weeks to determine efficacy of drug, but in practice some patients may

require up to 16–20 weeks to show a good response, especially on cognitive symptoms

If It Works

- Most often reduces positive symptoms but does not eliminate them
- Can improve negative symptoms, as well as aggressive, cognitive, and affective symptoms in schizophrenia
- Most schizophrenia patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third
- Perhaps 5–15% of schizophrenia patients can experience an overall improvement of greater than 50–60%, especially when receiving stable treatment for more than a year
- Such patients are considered super-responders or “awakeners” since they may be well enough to be employed, live independently, and sustain long-term relationships
- Many bipolar patients may experience a reduction of symptoms by half or more
- Continue treatment until reaching a plateau of improvement
- After reaching a satisfactory plateau, continue treatment for at least a year after first episode of psychosis
- For second and subsequent episodes of psychosis, treatment may need to be indefinite
- Even for first episodes of psychosis, it may be preferable to continue treatment
- Treatment may not only reduce mania but also prevent recurrences of mania in bipolar disorder

If It Doesn't Work

- Try one of the other atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, iloperidone, amisulpride, lurasidone)
- If 2 or more antipsychotic monotherapies do not work, consider clozapine
- Some patients may require treatment with a conventional antipsychotic
- If no first-line atypical antipsychotic is effective, consider higher doses or augmentation with valproate or lamotrigine
- Consider noncompliance and switch to another antipsychotic with fewer side effects or to an antipsychotic that can be given by depot injection

- Consider initiating rehabilitation and psychotherapy such as cognitive remediation
- Consider presence of concomitant drug abuse



Best Augmenting Combos for Partial Response or Treatment Resistance

- Valproic acid (valproate, divalproex, divalproex ER)
- Other mood-stabilizing anticonvulsants (carbamazepine, oxcarbazepine, lamotrigine)
- Lithium
- Benzodiazepines

Tests

Before starting an a typical antipsychotic

- Weigh all patients and track BMI during treatment
- Get baseline personal and family history of diabetes, obesity, dyslipidemia, hypertension, and cardiovascular disease
- Get waist circumference (at umbilicus), blood pressure, fasting plasma glucose, and fasting lipid profile
- Determine if the patient is
 - overweight (BMI 25.0–29.9)
 - obese (BMI >30)
 - has pre-diabetes (fasting plasma glucose 100–125 mg/dL)
 - has diabetes (fasting plasma glucose >126 mg/dL)
 - has hypertension (BP >140/90 mm Hg)
 - has dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol)
- Treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management

Monitoring after starting an atypical antipsychotic

- BMI monthly for 3 months, then quarterly
- Consider monitoring fasting triglycerides monthly for several months in patients at high risk for metabolic complications and when initiating or switching antipsychotics
- Blood pressure, fasting plasma glucose, fasting lipids within 3 months and then annually, but earlier and more frequently for patients with diabetes or who have gained >5% of initial weight
- Treat or refer for treatment and consider switching to another atypical antipsychotic

for patients who become overweight, obese, pre-diabetic, diabetic, hypertensive, or dyslipidemic while receiving an atypical antipsychotic

- Even in patients without known diabetes, be vigilant for the rare but life-threatening onset of diabetic ketoacidosis, which always requires immediate treatment, by monitoring for the rapid onset of polyuria, polydipsia, weight loss, nausea, vomiting, dehydration, rapid respiration, weakness and clouding of sensorium, even coma
- Patients with low white blood cell count (WBC) or history of drug-induced leucopenia/neutropenia should have complete blood count (CBC) monitored frequently during the first few months and asenapine should be discontinued at the first sign of decline in WBC in the absence of other causative factors

SIDE EFFECTS

How Drug Causes Side Effects

- By blocking alpha 1 adrenergic receptors, it can cause dizziness, sedation, and hypotension
- By blocking dopamine 2 receptors in the striatum, it can cause motor side effects
- By blocking dopamine 2 receptors in the pituitary, it can theoretically cause elevations in prolactin
- Mechanism of weight gain and increased incidence of diabetes and dyslipidemia with atypical antipsychotics is unknown

Notable Side Effects

- Sedation, dizziness
- Oral hypoesthesia
- Application site reactions: oral ulcers, blisters, peeling/sloughing, inflammation
- Extrapyramidal symptoms, akathisia
- May increase risk for diabetes and dyslipidemia
- Rare tardive dyskinesia (much reduced risk compared to conventional antipsychotics)
- Orthostatic hypotension



Life-Threatening or Dangerous Side Effects

- Type 1 hypersensitivity reactions (anaphylaxis, angioedema, low blood pressure, rapid heart rate, swollen tongue, difficulty breathing, wheezing, rash)

- Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking atypical antipsychotics
- Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis
- Rare neuroleptic malignant syndrome (much reduced risk compared to conventional antipsychotics)
- Rare seizures

Weight Gain



- Occurs in a significant minority
- May be less than for some antipsychotics, more than for others

Sedation



- Many experience and/or can be significant in amount

What to Do About Side Effects

- Wait
- Wait
- Wait
- Anticholinergics may reduce motor side effects when present
- Weight loss, exercise programs, and medical management for high BMIs, diabetes, dyslipidemia
- Switch to another atypical antipsychotic

Best Augmenting Agents for Side Effects

- Benztrapine or trihexyphenidyl for motor side effects
- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 10–20 mg/day in 2 divided doses for schizophrenia
- 10–20 mg/day in 2 divided doses for bipolar mania

Dosage Forms

- Sublingual tablet 2.5 mg, 5 mg, 10 mg

How to Dose

- Must be administered sublingually; patients may not eat or drink for 10 minutes following administration
- Schizophrenia: initial 10 mg/day in 2 divided doses; maximum dose generally 20 mg/day in 2 divided doses; limited experience with once daily administration
- Bipolar mania (adults, monotherapy): initial 20 mg/day in 2 divided doses; can reduce dose to 10 mg/day in 2 divided doses if there are adverse effects
- Bipolar mania (adults, adjunct): initial 10 mg/day in 2 divided doses; can increase to 20 mg/day in 2 divided doses
- Bipolar mania (children, monotherapy): initial 5 mg/day in 2 divided doses; after 3 days can increase to 10 mg/day in 2 divided doses; after 3 more days can increase to 20 mg/day in 2 divided doses
- Pediatric patients may be more sensitive to dystonia with initial dosing if the recommended titration schedule is not followed



Dosing Tips

- Asenapine is not absorbed after swallowing (less than 2% bioavailable orally) and thus must be administered sublingually (35% bioavailable), as swallowing would render asenapine inactive
- Patients should be instructed to place the tablet under the tongue and allow it to dissolve completely, which will occur in seconds; tablet should not be divided, crushed, chewed, or swallowed
- Patients may not eat or drink for 10 minutes following sublingual administration so that the drug in the oral cavity can be absorbed locally and not washed into the stomach (where it would not be absorbed)
- Once daily use seems theoretically possible because the half-life of asenapine is 13–39 hours, but this has not been extensively studied and may be limited by the need to expose the limited sublingual surface area to a limited amount of sublingual drug dosage
- Some patients may respond to doses greater than 20 mg/day but no single administration should be greater than 10 mg, thus necessitating 3 or 4 separate daily doses

- Due to rapid onset of action, can be used as a rapid acting "prn" or "as needed" dose for agitation or transient worsening of psychosis or mania instead of an injection
- Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³

Overdose

- Agitation, confusion

Long-Term Use

- Not studied, but long-term maintenance treatment is often necessary for schizophrenia and bipolar disorder

Habit Forming

- No

How to Stop

- Down-titration, over 2–4 weeks when possible, especially when simultaneously beginning a new antipsychotic while switching (i.e., cross-titration)
- Rapid discontinuation could theoretically lead to rebound psychosis and worsening of symptoms

Pharmacokinetics

- Half-life 13–39 hours
- Inhibits CYP450 2D6
- Substrate for CYP450 1A2
- Optimal bioavailability is with sublingual administration (~35%); if food or liquid is consumed within 10 minutes of administration bioavailability decreases to 28%; bioavailability decreases to 2% if swallowed



Drug Interactions

- May increase effects of antihypertensive agents
- May antagonize levodopa, dopamine agonists
- CYP450 1A2 inhibitors (e.g., fluvoxamine) can raise asenapine levels
- Via CYP450 2D6 inhibition, asenapine could theoretically interfere with the analgesic effects of codeine, and increase the plasma levels of some beta blockers and of atomoxetine
- Via CYP450 2D6 inhibition, asenapine could theoretically increase concentrations of thioridazine and cause dangerous cardiac arrhythmias



Other Warnings/ Precautions

- Use with caution in patients with conditions that predispose to hypotension (dehydration, overheating)
- Dysphagia has been associated with antipsychotic use, and asenapine should be used cautiously in patients at risk for aspiration pneumonia

Do Not Use

- If there is a proven allergy to asenapine

SPECIAL POPULATIONS

Renal Impairment

- Dose adjustment not generally necessary

Hepatic Impairment

- No dose adjustment necessary for mild to moderate impairment
- Not recommended for patients with severe hepatic impairment

Cardiac Impairment

- Drug should be used with caution because of risk of orthostatic hypotension

Elderly

- Some patients may tolerate lower doses better
- Although atypical antipsychotics are commonly used for behavioral disturbances in dementia, no agent has been approved for treatment of elderly patients with dementia-related psychosis
- Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo, and also have an increased risk of cerebrovascular events



Children and Adolescents

- Approved to treat acute manic/mixed episodes of bipolar I disorder in children ages 10 and older
- Children and adolescents using asenapine may need to be monitored more often than adults



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels; including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- There is a risk of abnormal muscle movements and withdrawal symptoms in newborns whose mothers took an antipsychotic during the third trimester; symptoms may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty feeding
- In animal studies, asenapine increased post-implantation loss and decreased pup weight and survival at doses similar to or less than recommended clinical doses; there was no increase in the incidence of structural abnormalities
- Psychotic symptoms may worsen during pregnancy and some form of treatment may be necessary
- Asenapine may be preferable to anticonvulsant mood stabilizers if treatment is required during pregnancy
- National Pregnancy Registry for Atypical Antipsychotics: 1-866-961-2388 or <http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/>

Breast Feeding

- Unknown if asenapine is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- Recommended either to discontinue drug or bottle feed
- Infants of women who choose to breast feed while on asenapine should be monitored for possible adverse effects

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients requiring rapid onset of antipsychotic action without dosage titration

Potential Disadvantages

- Patients who are less likely to be adherent

Primary Target Symptoms

- Positive symptoms of psychosis
- Negative symptoms of psychosis
- Cognitive symptoms
- Unstable mood (both depression and mania)
- Aggressive symptoms



Pearls

- Asenapine's chemical structure is related to the antidepressant mirtazapine and it shares many of the same pharmacologic binding properties of mirtazapine plus many others
- Not approved for depression, but binding properties suggest potential use in treatment-resistant and bipolar depression
- Sublingual administration may require prescribing asenapine to reliable, adherent patients, or those who have someone who can supervise drug administration
- Patients with inadequate responses to atypical antipsychotics may benefit from determination of plasma drug levels and, if low, a dosage increase even beyond the usual prescribing limits
- Patients with inadequate responses to atypical antipsychotics may also benefit from a trial of augmentation with a conventional antipsychotic or switching to a conventional antipsychotic
- However, long-term polypharmacy with a combination of a conventional antipsychotic with an atypical antipsychotic may combine their side effects without clearly augmenting the efficacy of either
- For treatment-resistant patients, especially those with impulsivity, aggression, violence, and self-harm, long-term polypharmacy with 2 atypical antipsychotics or with 1 atypical antipsychotic and 1 conventional

ASENAPINE (continued)

- antipsychotic may be useful or even necessary while closely monitoring
- In such cases, it may be beneficial to combine 1 depot antipsychotic with 1 oral antipsychotic

- Although a frequent practice by some prescribers, adding 2 conventional antipsychotics together has little rationale and may reduce tolerability without clearly enhancing efficacy

THE ART OF SWITCHING



Switching from Oral Antipsychotics to Asenapine

- With aripiprazole, amisulpride, and paliperidone ER, immediate stop is possible; begin asenapine at middle dose
- With risperidone, ziprasidone, iloperidone, and lurasidone: begin asenapine gradually, titrating over at least 2 weeks to allow patients to become tolerant to the sedating effect

* May need to taper clozapine slowly over 4 weeks or longer



Suggested Reading

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Shahid M, Walker GB, Zorn SH, Wong EH. Asenapine: a novel psychopharmacologic

agent with a unique human receptor signature. *J Psychopharmacol* 2009;23(1):65–73.

Tarazi F, Stahl SM. Iloperidone, asenapine and lurasidone: a primer on their current status. *Exp Opin Pharmacother* 2012;13(13):1911–22.

THERAPEUTICS

Brands • Strattera

see index for additional brand names

Generic? Yes**Class**

- Neuroscience-based Nomenclature: norepinephrine reuptake inhibitor (N-RI)
- Selective norepinephrine reuptake inhibitor (NRI)

Commonly Prescribed for

(bold for FDA approved)

- **Attention deficit hyperactivity disorder (ADHD) in adults and children over 6**
- Treatment-resistant depression

**How the Drug Works**

- Boosts neurotransmitter norepinephrine/noradrenaline and may also increase dopamine in prefrontal cortex
- Blocks norepinephrine reuptake pumps, also known as norepinephrine transporters
- Presumably this increases noradrenergic neurotransmission
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, atomoxetine can also increase dopamine neurotransmission in this part of the brain

How Long Until It Works

- ✳ Onset of therapeutic actions in ADHD can be seen as early as the first day of dosing
- Therapeutic actions may continue to improve for 8–12 weeks
 - If it is not working within 6–8 weeks, it may not work at all

If It Works

- The goal of treatment of ADHD is reduction of symptoms of inattentiveness, motor hyperactivity, and/or impulsiveness that disrupt social, school, and/or occupational functioning
- Continue treatment until all symptoms are under control or improvement is stable and then continue treatment indefinitely as long as improvement persists
- Reevaluate the need for treatment periodically

- Treatment for ADHD begun in childhood may need to be continued into adolescence and adulthood if continued benefit is documented

If It Doesn't Work

- Consider adjusting dose or switching to another agent
- Consider behavioral therapy
- Consider the presence of noncompliance and counsel patient and parents
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., bipolar disorder, substance abuse, medical illness, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require atomoxetine discontinuation and a switch to a mood stabilizer

**Best Augmenting Combos for Partial Response or Treatment Resistance**

- ✳ Best to attempt other monotherapies prior to augmenting
- SSRIs, SNRIs, or mirtazapine for treatment-resistant depression (use combinations of antidepressants with atomoxetine with caution as this may theoretically activate bipolar disorder and suicidal ideation)
 - Mood stabilizers or atypical antipsychotics for comorbid bipolar disorder
 - For the expert, can combine with modafinil, methylphenidate, or amphetamine for ADHD

Tests

- None recommended for healthy patients
- May be prudent to monitor blood pressure and pulse when initiating treatment and until dosage increments have stabilized

SIDE EFFECTS

How Drug Causes Side Effects

- Norepinephrine increases in parts of the brain and body and at receptors other than those that cause therapeutic actions (e.g., unwanted actions of norepinephrine on acetylcholine release causing decreased appetite, increased heart rate and blood pressure, dry mouth, urinary retention, etc.)

- Most side effects are immediate but often go away with time
- Lack of enhancing dopamine activity in limbic areas theoretically explains atomoxetine's lack of abuse potential

Notable Side Effects

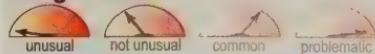
- Sedation, fatigue (particularly in children)
- Decreased appetite
- Rare priapism
- Increased heart rate (6–9 beats/min)
- Increased blood pressure (2–4 mm Hg)
- Insomnia, dizziness, anxiety, agitation, aggression, irritability
- Dry mouth, constipation, nausea, vomiting, abdominal pain, dyspepsia
- Urinary hesitancy, urinary retention (older men)
- Dysmenorrhea, sweating
- Sexual dysfunction (men: decreased libido, erectile disturbance, impotence, ejaculatory dysfunction, abnormal orgasm; women: decreased libido, abnormal orgasm)



Life-Threatening or Dangerous Side Effects

- Increased heart rate and hypertension
- Orthostatic hypotension
- Severe liver damage (rare)
- Hypomania and, theoretically, rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Reported but not expected
- Patients may experience weight loss

Sedation



- Occurs in significant minority, particularly in children

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose

- If giving once daily, can change to split dose twice daily
- If atomoxetine is sedating, take at night to reduce daytime drowsiness
- In a few weeks, switch or add other drugs

Best Augmenting Agents for Side Effects

- For urinary hesitancy, give an alpha 1 blocker such as tamsulosin
- Often best to try another monotherapy prior to resorting to augmentation strategies to treat side effects
- Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of atomoxetine

DOSING AND USE

Usual Dosage Range

- 0.5–1.2 mg/kg/day in children up to 70 kg; 40–100 mg/day in adults

Dosage Forms

- Capsule 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg

How to Dose

- For children 70 kg or less: initial dose 0.5 mg/kg per day; after 7 days can increase to 1.2 mg/kg per day either once in the morning or divided; maximum dose 1.4 mg/kg per day or 100 mg/day, whichever is less
- For adults and children over 70 kg: initial dose 40 mg/day; after 7 days can increase to 80 mg/day once in the morning or divided; after 2–4 weeks can increase to 100 mg/day if necessary; maximum daily dose 100 mg



Dosing Tips

- Can be given once a day in the morning
- Efficacy with once daily dosing despite a half-life of 5 hours suggests therapeutic effects persist beyond direct pharmacologic effects, unlike stimulants whose effects are generally closely correlated with plasma drug levels
- Once daily dosing may increase gastrointestinal side effects
- Lower starting dose allows detection of those patients who may be especially sensitive to side effects such as tachycardia and increased blood pressure
- Patients especially sensitive to the side effects of atomoxetine may include those individuals deficient in the enzyme that metabolizes atomoxetine, CYP450 2D6 (i.e., 7% of Caucasians and 2% of African Americans)
- In such individuals, drug should be titrated slowly to tolerability and effectiveness
- Other individuals may require up to 1.8 mg/kg total daily dose

Overdose

- No fatalities have been reported as monotherapy; sedation, agitation, hyperactivity, abnormal behavior, gastrointestinal symptoms

Long-Term Use

- Safe

Habit Forming

- No

How to Stop

- Taper not necessary

Pharmacokinetics

- Metabolized by CYP450 2D6
- Half-life approximately 5 hours
- Food does not affect absorption



Drug Interactions

- Tramadol increases the risk of seizures in patients taking an antidepressant
- Plasma concentrations of atomoxetine may be increased by drugs that inhibit CYP450 2D6 (e.g., paroxetine, fluoxetine), so atomoxetine dose may need to be reduced if coadministered

- Coadministration of atomoxetine and oral or IV albuterol may lead to increases in heart rate and blood pressure
- Coadministration with methylphenidate does not increase cardiovascular side effects beyond those seen with methylphenidate alone
- Use with caution with MAOIs, including 14 days after MAOIs are stopped (for the expert)



Other Warnings/ Precautions

- Growth (height and weight) should be monitored during treatment with atomoxetine; for patients who are not growing or gaining weight satisfactorily, interruption of treatment should be considered
- Use with caution in patients with hypertension, tachycardia, cardiovascular disease, or cerebrovascular disease
- Use with caution in patients with bipolar disorder
- Use with caution in patients with urinary retention, benign prostatic hypertrophy
- Rare reports of hepatotoxicity; although causality has not been established, atomoxetine should be discontinued in patients who develop jaundice or other evidence of significant liver dysfunction
- Use with caution with antihypertensive drugs
- Increased risk of sudden death has been reported in children with structural cardiac abnormalities or other serious heart conditions
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is taking an MAOI (except as noted under drug interactions)

- If patient has pheochromocytoma or history of pheochromocytoma
- If patient has a severe cardiovascular disorder that might deteriorate with clinically important increases in heart rate and blood pressure
- If patient has angle-closure glaucoma
- If there is a proven allergy to atomoxetine

- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Some animal studies have shown adverse effects
- Use in women of childbearing potential requires weighing potential benefits to the mother against potential risks to the fetus
- For women of childbearing potential, atomoxetine should generally be discontinued before anticipated pregnancies

Breast Feeding

- Unknown if atomoxetine is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- Recommend either to discontinue drug or bottle feed



Children and Adolescents

- Approved to treat ADHD in children over age 6
- Recommended target dose is 1.2 mg/kg per day
- Do not use in children with structural cardiac abnormalities or other serious cardiac problems
- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- No known abuse potential

Potential Disadvantages

- May not act as rapidly as stimulants when initiating treatment in some patients

Primary Target Symptoms

- Concentration, attention span
- Motor hyperactivity
- Depressed mood



Pearls

- ✿ Unlike other agents approved for ADHD, atomoxetine does not have abuse potential and is not a scheduled substance
- ✿ Despite its name as a selective norepinephrine reuptake inhibitor, atomoxetine enhances both dopamine and norepinephrine in frontal cortex, presumably accounting for its therapeutic actions on attention and concentration
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, atomoxetine can increase dopamine as well as norepinephrine in this part of the brain, presumably causing therapeutic actions in ADHD
- Since dopamine is inactivated by dopamine reuptake in nucleus accumbens, which largely lacks norepinephrine transporters, atomoxetine does not increase dopamine in this part of the brain, presumably explaining why atomoxetine lacks abuse potential
- Atomoxetine's known mechanism of action as a selective norepinephrine reuptake

inhibitor suggests its efficacy as an antidepressant

- Pro-noradrenergic actions may be theoretically useful for the treatment of chronic pain
- Atomoxetine's mechanism of action and its potential antidepressant actions suggest it has the potential to destabilize latent or undiagnosed bipolar disorder, similar to the known actions of proven antidepressants
- Thus, administer with caution to ADHD patients who may also have bipolar disorder
- Unlike stimulants, atomoxetine may not exacerbate tics in Tourette's syndrome patients with comorbid ADHD
- Urinary retention in men over 50 with borderline urine flow has been observed with other agents with potent norepinephrine reuptake blocking properties (e.g., reboxetine, milnacipran), so administer atomoxetine with caution to these patients
- Atomoxetine was originally called tomoxetine but the name was changed to avoid potential confusion with tamoxifen, which might lead to errors in drug dispensing



Suggested Reading

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two randomized, placebo-controlled studies. *Biol Psychiatry* 2003;53(2):112–20.

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THERAPEUTICS

Brands • Rexulti

see index for additional brand names

Generic? No**Class**

- Dopamine partial agonist (dopamine stabilizer, atypical antipsychotic, third-generation antipsychotic; sometimes included as a second-generation antipsychotic; also a potential mood stabilizer)

Commonly Prescribed for

(bold for FDA approved)

- **Schizophrenia**
- **Treatment-resistant depression (adjunct)**
- Acute mania/mixed mania
- Other psychotic disorders
- Bipolar maintenance
- Bipolar depression
- Behavioral disturbances in dementia
- Behavioral disturbances in children and adolescents
- Disorders associated with problems with impulse control

**How the Drug Works**

- Partial agonism at dopamine 2 receptors
- Theoretically reduces dopamine output when dopamine concentrations are high, thus improving positive symptoms and mediating antipsychotic actions
- Theoretically increases dopamine output when dopamine concentrations are low, thus improving cognitive, negative, and mood symptoms
- Partial agonist at 5HT1A receptors, which may be beneficial for mood, anxiety, and cognition in a number of disorders
- Blockade of serotonin type 2A receptors may contribute at clinical doses to cause enhancement of dopamine release in certain brain regions, thus reducing motor side effects and possibly improving cognitive and affective symptoms
- Blockade of alpha 1B receptors may reduce motor side effects such as akathisia
- Blockade of alpha 2C receptors may contribute to antidepressant actions

- Actions at dopamine 3 receptors could theoretically contribute to brexpiprazole's efficacy
- Blocks serotonin 7 receptors, which may be beneficial for mood, cognitive impairment, and negative symptoms in schizophrenia, and also in bipolar disorder and major depressive disorder

How Long Until It Works

- Psychotic symptoms can improve within 1 week, but it may take several weeks for full effect on behavior as well as on cognition
- For psychosis, classically recommended to wait at least 4–6 weeks to determine efficacy of drug, but in practice some patients may require up to 16–20 weeks to show a good response, especially on cognitive impairment and functional outcome
- For depression, onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks

If It Works (for Schizophrenia)

- Most often reduces positive symptoms but does not eliminate them
- Can improve negative symptoms, as well as aggressive, cognitive, and affective symptoms in schizophrenia
- Most schizophrenia patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third
- Perhaps 5–15% of schizophrenia patients can experience an overall improvement of greater than 50–60%, especially when receiving stable treatment for more than a year
- Such patients are considered super-responders or "awakeners" since they may be well enough to be employed, live independently, and sustain long-term relationships
- Continue treatment until reaching a plateau of improvement
- After reaching a satisfactory plateau, continue treatment for at least a year after first episode of psychosis
- For second and subsequent episodes of psychosis, treatment may need to be indefinite
- Even for first episodes of psychosis, it may be preferable to continue treatment

If It Works (for Depression)

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Continue treatment until all symptoms are gone (remission) or significantly reduced
- Once symptoms are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite

If It Doesn't Work (for Schizophrenia)

- Try one of the other atypical antipsychotics
- If 2 or more antipsychotic monotherapies do not work, consider clozapine
- Some patients may require treatment with a conventional antipsychotic
- If no first-line atypical antipsychotic is effective, consider higher doses or augmentation with valproate or lamotrigine
- Consider noncompliance and switch to another antipsychotic with fewer side effects or to an antipsychotic that can be given by depot injection
- Consider initiating rehabilitation and psychotherapy
- Consider presence of concomitant drug abuse

If It Doesn't Work (for Depression)

- Some patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some patients who have an initial response may relapse even though they continue treatment, sometimes called "poop-out"
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder



Best Augmenting Combos for Partial Response or Treatment Resistance

- For depression, brexipiprazole is itself an augmenting agent
- Valproic acid (valproate, divalproex, divalproex ER)
- Mood stabilizing anticonvulsants (carbamazepine, oxcarbazepine, lamotrigine)
- Lithium
- Benzodiazepines

Tests

Before starting any atypical antipsychotic

- Weigh all patients and track BMI during treatment
- Get baseline personal and family history of diabetes, obesity, dyslipidemia, hypertension, and cardiovascular disease
- Get waist circumference (at umbilicus), blood pressure, fasting plasma glucose, and fasting lipid profile
- Determine if the patient is
 - overweight (BMI 25.0–29.9)
 - obese (BMI ≥ 30)
 - has pre-diabetes (fasting plasma glucose 100–125 mg/dL)
 - has diabetes (fasting plasma glucose ≥ 126 mg/dL)
 - has hypertension (BP $>140/90$ mmHg)
 - has dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol)
- Treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management

Monitoring after starting any atypical antipsychotic

- BMI monthly for 3 months, then quarterly
- Consider monitoring fasting triglycerides monthly for several months in patients at high risk for metabolic complications and when initiating or switching antipsychotics
- Blood pressure, fasting plasma glucose, fasting lipids within 3 months and then annually, but earlier and more frequently for patients with diabetes or who have gained $>5\%$ of initial weight

- Treat or refer for treatment and consider switching to another atypical antipsychotic for patients who become overweight, obese, pre-diabetic, diabetic, hypertensive, or dyslipidemic while receiving an atypical antipsychotic
- * Even in patients without known diabetes, be vigilant for the rare but life-threatening onset of diabetic ketoacidosis, which always requires immediate treatment, by monitoring for the rapid onset of polyuria, polydipsia, weight loss, nausea, vomiting, dehydration, rapid respiration, weakness and clouding of sensorium, even coma**
- Patients with low white blood cell count (WBC) or history of drug-induced leukopenia/neutropenia should have complete blood count (CBC) monitored frequently during the first few months and brexpiprazole should be discontinued at the first sign of decline in WBC in the absence of other causative factors

SIDE EFFECTS

How Drug Causes Side Effects

- By blocking alpha 1 adrenergic receptors, it can cause dizziness, sedation, and hypotension
- Partial agonist actions at dopamine 2 receptors in the striatum can cause motor side effects, such as akathisia
- Partial agonist actions at dopamine 2 receptors and 5HT1A receptors can also cause nausea, occasional vomiting, and activating side effects
- Mechanism of weight gain and increased incidence of diabetes and dyslipidemia with atypical antipsychotics is unknown

Notable Side Effects

- Weight gain
- Akathisia (dose dependent), restlessness (dose dependent), anxiety
- Sedation, headache
- Theoretical risk of tardive dyskinesia



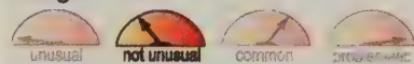
Life-Threatening or Dangerous Side Effects

- Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been

reported in patients taking atypical antipsychotics

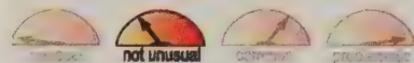
- Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis
- Rare neuroleptic malignant syndrome (much reduced risk compared to conventional antipsychotics)
- Rare seizures

Weight Gain



- Occurs in a significant minority

Sedation



- Occurs in a significant minority

What to Do About Side Effects

- Wait
- Wait
- Wait
- Anticholinergics may reduce motor side effects when present
- Weight loss, exercise programs, and medical management for high BMIs, diabetes, dyslipidemia
- Switch to another atypical antipsychotic

Best Augmenting Agents for Side Effects

- Benztropine or trihexyphenidyl for motor side effects
- Beta blockers or sometimes benzodiazepines for akathisia
- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- Schizophrenia: 2–4 mg once daily
- Depression: 2 mg once daily

Dosage Forms

- Tablet 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg

How to Dose

- Schizophrenia: Initial 1 mg once daily for days 1–4; increase to 2 mg once daily for

days 5–7; increase to 4 mg once daily on day 8; maximum dose 4 mg once daily

- Depression: Initial 0.5–1 mg once daily; increase in weekly intervals up to 1 mg once daily and then up to 2 mg once daily; maximum dose 3 mg once daily



Dosing Tips

- Can be taken with or without food

Overdose

- Limited experience

Long-Term Use

- Safety and efficacy demonstrated in schizophrenia in a maintenance study lasting over 1 year
- Should periodically reevaluate long-term usefulness in individual patients, but treatment may need to continue for many years in patients with schizophrenia or treatment-resistant depression

Habit Forming

- No

How to Stop

- Because clinical experience is lacking, down-titration may be prudent, especially when simultaneously beginning a new antipsychotic while switching (i.e., cross-titration)
- However, the long half-life suggests that it may be possible to stop brexpiprazole abruptly
- The method for stopping brexpiprazole can vary depending on which agent is being switched to; see switching guidelines of individual agents for how to stop brexpiprazole
- Rapid discontinuation could theoretically lead to rebound psychosis and worsening of symptoms, but less likely with brexpiprazole due to its long half-life

Pharmacokinetics

- Mean half-life 91 hours (brexpiprazole) and 86 hours (major metabolite DM-3411)
- Metabolized primarily by CYP450 2D6 and CYP450 3A4



Drug Interactions

- In patients receiving a strong/moderate CYP450 3A4 inhibitor (e.g., ketoconazole), brexpiprazole should be administered at half the usual dose
- In patients receiving a strong CYP450 3A4 inducer (e.g., carbamazepine), brexpiprazole should be administered at double the usual dose
- In patients with schizophrenia who are receiving a strong/moderate CYP450 2D6 inhibitor (e.g., quinidine) or who are known CYP450 2D6 poor metabolizers, brexpiprazole should be administered at half the usual dose
- However, clinical trials in major depressive disorder took into account the potential concomitant administration of strong CYP450 2D6 inhibitors (e.g., paroxetine, fluoxetine), so the dose of brexpiprazole does not need to be adjusted in these cases
- In patients receiving both a strong/moderate CYP3A4 inhibitor and a strong/moderate CYP450 2D6 inhibitor, brexpiprazole should be administered at one quarter the usual dose
- In patients receiving a strong/moderate CYP3A4 inhibitor who are known CYP450 2D6 poor metabolizers, brexpiprazole should be administered at one quarter the usual dose
- May increase effects of antihypertensive agents
- May antagonize levodopa, dopamine agonists



Other Warnings/ Precautions

- Use with caution in patients with conditions that predispose to hypotension (dehydration, overheating)
- Dysphagia has been associated with antipsychotic use, and brexpiprazole should be used cautiously in patients at risk for aspiration pneumonia

Do Not Use

- If there is a proven allergy to brexpiprazole

SPECIAL POPULATIONS

Renal Impairment

- Moderate, severe, or end-stage: maximum recommended dose for depression is 2 mg once daily and for schizophrenia is 3 mg once daily

Hepatic Impairment

- Moderate to severe: maximum recommended dose for depression is 2 mg once daily and for schizophrenia is 3 mg once daily

Cardiac Impairment

- Use in patients with cardiac impairment has not been studied, so use with caution

Elderly

- Some elderly patients may tolerate lower doses better
- Although atypical antipsychotics are commonly used for behavioral disturbances in dementia, no agent has been approved for treatment of elderly patients with dementia-related psychosis
- Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo, and also have an increased risk of cerebrovascular events



Children and Adolescents

- Safety and efficacy have not been established
- Children and adolescents using brexpiprazole may need to be monitored more often than adults



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women

- In animal studies, brexpiprazole did not demonstrate teratogenicity
- There is a risk of abnormal muscle movements and withdrawal symptoms in newborns whose mothers took an antipsychotic during the third trimester; symptoms may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty feeding
- Psychotic symptoms may worsen during pregnancy and some form of treatment may be necessary
- Brexipiprazole may be preferable to anticonvulsant mood stabilizers if treatment is required during pregnancy
- National Pregnancy Registry for Atypical Antipsychotics: 1-866-961-2388 or <http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/>

Breast Feeding

- Unknown if brexpiprazole is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- Recommended either to discontinue drug or bottle feed unless the potential benefit to the mother justifies the potential risk to the child
- Infants of women who choose to breast feed while on brexpiprazole should be monitored for possible adverse effects

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- For patients who do not tolerate aripiprazole

Potential Disadvantages

- Expensive

Primary Target Symptoms

- Positive symptoms of psychosis
- Negative symptoms of psychosis
- Cognitive symptoms
- Unstable mood and depression
- Aggressive symptoms



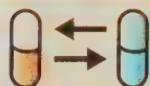
Pearls

- Approved as an adjunct treatment for depression

BREXPIPRAZOLE (continued)

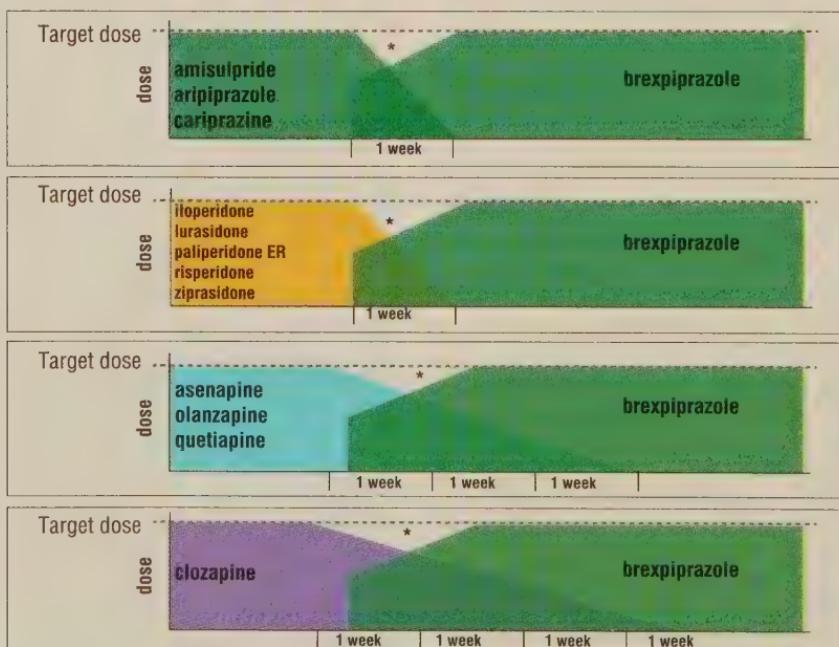
- Animal data suggest that brexpiprazole may improve cognitive impairment in schizophrenia
- Brexpiprazole is also being studied in clinical trials in attention deficit hyperactivity disorder, post-traumatic stress disorder, and agitation associated with Alzheimer dementia
- Not approved for mania, but almost all atypical antipsychotics approved for acute treatment of schizophrenia have proven effective in the acute treatment of mania as well
- Pharmacological differences from aripiprazole suggest less akathisia with brexpiprazole, but no head-to-head trials
- Compared to aripiprazole, brexpiprazole has more potent binding of several receptor sites relative to dopamine 2 receptor binding, namely 5HT1A, 5HT2A, and alpha 1 receptors; however, the clinical significance of these differences is still under investigation

THE ART OF SWITCHING



Switching from Oral Antipsychotics to Brexpiprazole

- It is advisable to begin brexpiprazole at an intermediate dose and build the dose rapidly over 3–7 days
 - Clinical experience has shown that asenapine, quetiapine, and olanzapine should be tapered off slowly over a period of 3–4 weeks, to allow patients to readapt to the withdrawal of blocking cholinergic, histaminergic, and alpha 1 receptors
 - Clozapine should always be tapered off slowly, over a period of 4 weeks or more
- * Benzodiazepine or anticholinergic medication can be administered during cross-titration to help alleviate side effects such as insomnia, agitation, and/or psychosis





Suggested Reading

Correll CU, Skuban A, Ouyang J, et al. Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: a 6-week randomized, double-blind, placebo-controlled trial. *Am J Psychiatry* 2015;172(9):870–80.

Kane JM, Skuban A, Ouyang J, et al. A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. *Schizophr Res* 2015;164(1–3):127–35.

Maeda K, Lerdrup L, Sugino H, et al. Brexpiprazole II: antipsychotic-like and procognitive effects of a novel serotonin-dopamine activity modulator. *J Pharmacol Exp Ther* 2014;350(3):605–14.

Oosterhof CA, El Mansari M, Blier P. Acute effects of brexpiprazole on serotonin, dopamine, and norepinephrine systems: an in vivo electrophysiologic characterization. *J Pharmacol Exp Ther* 2014;351(3):585–95.

THERAPEUTICS

- Brands**
- Wellbutrin, Wellbutrin SR, Wellbutrin XL
 - Zyban
 - Aplenzin

Generic? Yes



Class

- Neuroscience-based Nomenclature: dopamine reuptake inhibitor and releaser (D-RIRe)
- NDRI (norepinephrine dopamine reuptake inhibitor); antidepressant; smoking cessation treatment

Commonly Prescribed for

(bold for FDA approved)

- Major depressive disorder (**bupropion, bupropion SR, and bupropion XL**)
- Seasonal affective disorder (**bupropion XL**)
- Nicotine addiction (**bupropion SR**)
- Bipolar depression
- Attention deficit /hyperactivity disorder (ADHD)
- Sexual dysfunction



How the Drug Works

- Boosts neurotransmitters norepinephrine/ noradrenaline and dopamine
- Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing norepinephrine neurotransmission
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, bupropion can increase dopamine neurotransmission in this part of the brain
- Blocks dopamine reuptake pump (dopamine transporter), presumably increasing dopaminergic neurotransmission

How Long Until It Works

- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment of depression is complete remission of current symptoms as well as prevention of future relapses
- Treatment of depression most often reduces or even eliminates symptoms, but is not a cure since symptoms can recur after medicine stopped
- Continue treatment of depression until all symptoms are gone (remission)
- Once symptoms of depression are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Treatment for nicotine addiction should consist of a single treatment for 6 weeks

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some patients who have an initial response may relapse even though they continue treatment, sometimes called “poop-out”
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer, although this may be a less frequent problem with bupropion than with other antidepressants



Best Augmenting Combos for Partial Response or Treatment Resistance

- Trazodone for residual insomnia
- Benzodiazepines for residual anxiety
- *** Can be added to SSRIs to reverse SSRI-induced sexual dysfunction, SSRI-induced apathy (use combinations of antidepressants with caution as this may**

- activate bipolar disorder and suicidal ideation)
- ✿ Can be added to SSRIs to treat partial responders
- ✿ Often used as an augmenting agent to mood stabilizers and/or atypical antipsychotics in bipolar depression
- Mood stabilizers or atypical antipsychotics can also be added to bupropion for psychotic depression or treatment-resistant depression
- Hypnotics for insomnia
- Mirtazapine, modafinil, atomoxetine (add with caution and at lower doses since bupropion could theoretically raise atomoxetine levels) both for residual symptoms of depression and attention deficit disorder

Tests

- Recommended to assess blood pressure at baseline and periodically during treatment

SIDE EFFECTS

How Drug Causes Side Effects

- Side effects are probably caused in part by actions of norepinephrine and dopamine in brain areas with undesired effects (e.g., insomnia, tremor, agitation, headache, dizziness)
- Side effects are probably also caused in part by actions of norepinephrine in the periphery with undesired effects (e.g., sympathetic and parasympathetic effects such as dry mouth, constipation, nausea, anorexia, sweating)
- Most side effects are immediate but often go away with time

Notable Side Effects

- Dry mouth, constipation, nausea, weight loss, anorexia, myalgia
- Insomnia, dizziness, headache, agitation, anxiety, tremor, abdominal pain, tinnitus
- Sweating, rash
- Hypertension



Life-Threatening or Dangerous Side Effects

- Rare seizures (higher incidence for immediate-release than for sustained-release; risk increases with doses above the recommended maximums; risk

increases for patients with predisposing factors)

- Anaphylactoid/anaphylactic reactions and Stevens-Johnson syndrome have been reported
- Hypomania (more likely in bipolar patients but perhaps less common than with some other antidepressants)
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Reported but not expected

✿ Patients may experience weight loss

Sedation



- Reported but not expected

What to Do About Side Effects

- Wait
- Wait
- Wait
- Keep dose as low as possible
- Take no later than mid-afternoon to avoid insomnia
- Switch to another drug

Best Augmenting Agents for Side Effects

- Often best to try another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
- Trazodone or a hypnotic for drug-induced insomnia
- Mirtazapine for insomnia, agitation, and gastrointestinal side effects
- Benzodiazepines or buspirone for drug-induced anxiety, agitation
- Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Activation and agitation may represent the induction of a bipolar state, especially

a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of bupropion

DOSING AND USE

Usual Dosage Range

- Bupropion: 225–450 mg in 3 divided doses (maximum single dose 150 mg)
- Bupropion SR: 200–450 mg in 2 divided doses (maximum single dose 200 mg)
- Bupropion XL: 150–450 mg once daily (maximum single dose 450 mg)
- Bupropion hydrobromide: 174–522 mg once daily (maximum single dose 522 mg)

Dosage Forms

- Bupropion: tablet 75 mg, 100 mg
- Bupropion SR (sustained-release): tablet 100 mg, 150 mg, 200 mg
- Bupropion XL (extended-release): tablet 150 mg, 300 mg, 450 mg
- Bupropion hydrobromide (extended-release): tablet 174 mg, 378 mg, 522 mg

How to Dose

- Depression: for bupropion immediate-release, dosing should be in divided doses, starting at 75 mg twice daily, increasing to 100 mg twice daily, then to 100 mg 3 times daily; maximum dose 450 mg per day
- Depression: for bupropion SR, initial dose 100 mg twice a day, increase to 150 mg twice a day after at least 3 days; wait 4 weeks or longer to ensure drug effects before increasing dose; maximum dose 400 mg total per day
- Depression: for bupropion XL, initial dose 150 mg once daily in the morning; can increase to 300 mg once daily after 4 days; maximum single dose 450 mg once daily
- Depression: for bupropion hydrobromide, initial dose 174 mg once daily in the morning; can increase to 522 mg administered as a single dose
- Nicotine addiction [for bupropion SR]: initial dose 150 mg/day once a day, increase to 150 mg twice a day after at least 3 days; maximum dose 300 mg/day; bupropion treatment should begin 1–2 weeks before smoking is discontinued



Dosing Tips

- XL formulation has replaced immediate release and SR formulations as the preferred option
- XL is best dosed once a day, whereas SR is best dosed twice daily, and immediate release is best dosed 3 times daily
- Dosing higher than 450 mg/day (400 mg/day SR) increases seizure risk
- Patients who do not respond to 450 mg/day should discontinue use or get blood levels of bupropion and its major active metabolite 6-hydroxy-bupropion
- If levels of parent drug and active metabolite are low despite dosing at 450 mg/day, experts can prudently increase dosing beyond the therapeutic range while monitoring closely, informing the patient of the potential risk of seizures and weighing risk/benefit ratios in difficult-to-treat patients
- When used for bipolar depression, it is usually as an augmenting agent to mood stabilizers, lithium, and/or atypical antipsychotics
- For smoking cessation, may be used in conjunction with nicotine replacement therapy
- Do not break or chew SR or XL tablets as this will alter controlled-release properties
- The more anxious and agitated the patient, the lower the starting dose, the slower the titration, and the more likely the need for a concomitant agent such as trazodone or a benzodiazepine
- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar disorder and switch to a mood stabilizer or an atypical antipsychotic

Overdose

- Rarely lethal; seizures, cardiac disturbances, hallucinations, loss of consciousness

Long-Term Use

- For smoking cessation, treatment for up to 6 months has been found effective
- For depression, treatment up to 1 year has been found to decrease rate of relapse

Habit Forming

- No
- Can be abused by individuals who crush and then snort or inject it

How to Stop

- Tapering is prudent to avoid withdrawal effects, but no well-documented tolerance, dependence, or withdrawal reactions

Pharmacokinetics

- Inhibits CYP450 2D6
- Parent half-life 10–14 hours
- Metabolite half-life 20–27 hours
- Food does not affect absorption



Drug Interactions

- Tramadol increases the risk of seizures in patients taking an antidepressant
- Can increase TCA levels; use with caution with TCAs or when switching from a TCA to bupropion
- Use with caution with MAOIs, including 14 days after MAOIs are stopped (for the expert)
- There is increased risk of hypertensive reaction if bupropion is used in conjunction with MAOIs or other drugs that increase norepinephrine
- There may be an increased risk of hypertension if bupropion is combined with nicotine replacement therapy
- Via CYP450 2D6 inhibition, bupropion could theoretically interfere with the analgesic actions of codeine, and increase the plasma levels of some beta blockers and of atomoxetine
- Via CYP450 2D6 inhibition, bupropion could theoretically increase concentrations of thioridazine and cause dangerous cardiac arrhythmias



Other Warnings/ Precautions

- Use cautiously with other drugs that increase seizure risk (TCAs, lithium, phenothiazines, thioxanthenes, some antipsychotics)
- Bupropion should be used with caution in patients taking levodopa or amantadine, as these agents can potentially enhance

dopamine neurotransmission and be activating

- Do not use if patient has severe insomnia
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents
- Discontinuing smoking may lead to pharmacokinetic or pharmacodynamic changes in other drugs the patient is taking, which could potentially require dose adjustment

Do Not Use

- Zyban or Aplenzin in combination with each other or with any formulation of Wellbutrin
- If patient has history of seizures
- If patient is anorexic or bulimic, either currently or in the past, but see Pearls
- If patient is abruptly discontinuing alcohol, sedative use, or anticonvulsant medication
- If patient has had recent head injury
- If patient has a nervous system tumor
- If patient is taking an MAOI (except as noted under Drug Interactions)
- If patient is taking thioridazine
- If there is a proven allergy to bupropion

SPECIAL POPULATIONS

Renal Impairment

- Lower initial dose, perhaps give less frequently
- Drug concentration may be increased
- Patient should be monitored closely

Hepatic Impairment

- Lower initial dose, perhaps give less frequently
- Patient should be monitored closely

- In severe hepatic cirrhosis, bupropion XL should be administered at no more than 150 mg every other day

Cardiac Impairment

- Limited available data
- Evidence of rise in supine blood pressure
- Use with caution

Elderly

- Some patients may tolerate lower doses better
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Safety and efficacy have not been established
- May be used for ADHD in children or adolescents
- May be used for smoking cessation in adolescents
- Preliminary research suggests efficacy in comorbid depression and ADHD
- Dosage may follow adult pattern for adolescents
- Children may require lower doses initially, with a maximum dose of 300 mg/day



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies

only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001

- Controlled studies have not been conducted in pregnant women
- Epidemiological studies do not indicate increased risk of congenital malformations overall or of cardiovascular malformations
- In animal studies, no clear evidence of teratogenicity has been observed; however, slightly increased incidences of fetal malformations and skeletal variations were observed in rabbit studies at doses approximately equal to and greater than the maximum recommended human doses, and greater and decreased fetal weights were observed in rat studies at doses greater than the maximum recommended human doses
- Pregnant women wishing to stop smoking may consider behavioral therapy before pharmacotherapy
- Not generally recommended for use during pregnancy, especially during first trimester
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy

Breast Feeding

- Some drug is found in mother's breast milk
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients, this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY**Potential Advantages**

- Retarded depression
- Atypical depression
- Bipolar depression
- Patients concerned about sexual dysfunction
- Patients concerned about weight gain

Potential Disadvantages

- Patients experiencing weight loss associated with their depression
- Patients who are excessively activated

Primary Target Symptoms

- Depressed mood
- Sleep disturbance, especially hypersomnia
- Cravings associated with nicotine withdrawal
- Cognitive functioning

**Pearls**

- ✿ May be effective if SSRIs have failed or for SSRI "poop-out"
- Less likely to produce hypomania than some other antidepressants
- ✿ May improve cognitive slowing/pseudodementia
- ✿ Reduces hypersomnia and fatigue
- Approved to help reduce craving during smoking cessation
- Anecdotal use in attention deficit disorder
- May cause sexual dysfunction only infrequently
- May exacerbate tics
- Bupropion may not be as effective in anxiety disorders as many other antidepressants

- Prohibition for use in eating disorders due to increased risk of seizures is related to past observations when bupropion immediate-release was dosed at especially high levels to low body weight patients with active anorexia nervosa
- Current practice suggests that patients of normal BMI without additional risk factors for seizures can benefit from bupropion, especially if given prudent doses of the XL formulation; such treatment should be administered by experts, and patients should be monitored closely and informed of the potential risks
- Recently approved hydrobromide salt formulation of bupropion may facilitate high dosing for difficult-to-treat patients, as it allows administration of single-pill doses up to 450 mg equivalence to bupropion hydrochloride salt (522 mg tablet), unlike bupropion hydrochloride controlled-release formulations for which the biggest dose in a single pill is 300 mg
- As bromide salts have anticonvulsant properties, hydrobromide salts of bupropion could theoretically reduce risk of seizures, but this has not been proven
- The active enantiomer of the principal active metabolite [(+)-6-hydroxy-bupropion] is in clinical development as a novel antidepressant
- The combination of bupropion and naltrexone has demonstrated efficacy as a treatment for obesity and is currently being evaluated in a long-term study to assess the cardiovascular health outcomes of this treatment
- Phase II trials of the combination of bupropion and zonisamide for the treatment of obesity have been completed

**Suggested Reading**

Clayton AH. Extended-release bupropion: an antidepressant with a broad spectrum of therapeutic activity? *Expert Opin Pharmacother* 2007;8(4):457–66.

Ferry L, Johnston JA. Efficacy and safety of bupropion SR for smoking cessation: data from clinical trials and five years of postmarketing experience. *Int J Clin Pract* 2003;57(3):224–30.

Foley KF, DeSanty KP, Kast RE. Bupropion: pharmacology and therapeutic applications. *Expert Rev Neurother* 2006;6(9):1249–65.

Jefferson JW, Pradko JF, Muir KT. Bupropion for major depressive disorder: pharmacokinetic and formulation considerations. *Clin Ther* 2005;27(11):1685–95.

Papakostas GI, Nutt DJ, Hallett LA, et al. Resolution of sleepiness and fatigue in major depressive disorder: a comparison of bupropion and the selective serotonin reuptake inhibitors. *Biol Psychiatry* 2006;60(12):1350–5.

THERAPEUTICS

Brands • BuSpar

see index for additional brand names

Generic? Yes



Class

- Neuroscience-based Nomenclature: serotonin receptor partial agonist (S-RPA)
- Anxiolytic (azapirone; serotonin 1A partial agonist; serotonin stabilizer)

Commonly Prescribed for

(bold for FDA approved)

- Management of anxiety disorders
- Short-term treatment of symptoms of anxiety
- Mixed anxiety and depression
- Treatment-resistant depression (adjunctive)



How the Drug Works

- Binds to serotonin type 1A receptors
- Partial agonist actions postsynaptically may theoretically diminish serotonergic activity and contribute to anxiolytic actions
- Partial agonist actions at presynaptic somatodendritic serotonin autoreceptors may theoretically enhance serotonergic activity and contribute to antidepressant actions

How Long Until It Works

- Generally takes within 2–4 weeks to achieve efficacy
- If it is not working within 6–8 weeks, it may require a dosage increase or it may not work at all

If It Works

- The goal of treatment is complete remission of symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Chronic anxiety disorders may require long-term maintenance with buspirone to control symptoms

If It Doesn't Work

- Consider switching to another agent (a benzodiazepine or antidepressant)



Best Augmenting Combos for Partial Response or Treatment Resistance

- Sedative hypnotic for insomnia
- Buspirone is often given as an augmenting agent to SSRIs or SNRIs

Tests

- None for healthy individuals

SIDE EFFECTS

How Drug Causes Side Effects

- Serotonin partial agonist actions in parts of the brain and body and at receptors other than those that cause therapeutic actions

Notable Side Effects

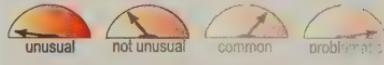
- Dizziness, headache, nervousness, sedation, excitement
- Nausea
- Restlessness



Life-Threatening or Dangerous Side Effects

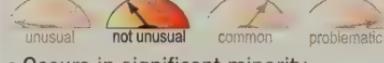
- Rare cardiac symptoms

Weight Gain



- Reported but not expected

Sedation



- Occurs in significant minority

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- Give total daily dose divided into 3, 4, or more doses
- Switch to another agent

Best Augmenting Agents for Side Effects

- Many side effects cannot be improved with an augmenting agent

DOSING AND USE**Usual Dosage Range**

- 20–30 mg/day

Dosage Forms

- Tablet 5 mg scored, 10 mg scored, 15 mg multiscored, 30 mg multiscored

How to Dose

- Initial 15 mg twice a day; increase in 5 mg/day increments every 2–3 days until desired efficacy is reached; maximum dose generally 60 mg/day

**Dosing Tips**

- Requires dosing 2–3 times a day for full effect
- Absorption is affected by food, so administration with or without food should be consistent

Overdose

- No deaths reported in monotherapy; sedation, dizziness, small pupils, nausea, vomiting

Long-Term Use

- Limited data suggest that it is safe

Habit Forming

- No

How to Stop

- Taper generally not necessary

Pharmacokinetics

- Metabolized primarily by CYP450 3A4
- Elimination half-life approximately 2–3 hours
- Absorption is affected by food

**Drug Interactions**

- Use with caution with MAOIs, including 14 days after MAOIs are stopped (for the expert)
- CYP450 3A4 inhibitors (e.g., fluoxetine, fluvoxamine, nefazodone) may reduce clearance of buspirone and raise its plasma levels, so the dose of buspirone may need to be lowered when given concomitantly with these agents
- CYP450 3A4 inducers (e.g., carbamazepine) may increase clearance of

buspirone, so the dose of buspirone may need to be raised

- Buspirone may increase plasma concentrations of haloperidol
- Buspirone may raise levels of nordiazepam, the active metabolite of diazepam, which may result in increased symptoms of dizziness, headache, or nausea

**Other Warnings/
Precautions**

- None

Do Not Use

- If patient is taking an MAOI (except as noted under Drug Interactions)
- If there is a proven allergy to buspirone

SPECIAL POPULATIONS**Renal Impairment**

- Use with caution
- Not recommended for patients with severe renal impairment

Hepatic Impairment

- Use with caution
- Not recommended for patients with severe hepatic impairment

Cardiac Impairment

- Buspirone has been used to treat hostility in patients with cardiac impairment

Elderly

- Some patients may tolerate lower doses better

**Children and Adolescents**

- Studies in children age 6–17 do not show significant reduction in anxiety symptoms in generalized anxiety disorder (GAD)
- Safety profile in children encourages use

**Pregnancy**

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter

categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001.

- Controlled studies have not been conducted in pregnant women
- Animal studies have not shown adverse effects
- Not generally recommended in pregnancy, but may be safer than some other options

Breast Feeding

- Some drug is found in mother's breast milk
- Trace amounts may be present in nursing children whose mothers are on buspirone
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Safety profile
- Lack of dependence, withdrawal
- Lack of sexual dysfunction or weight gain

Potential Disadvantages

- Takes 4 weeks for results, whereas benzodiazepines have immediate effects

Primary Target Symptoms

- Anxiety



Pearls

- Buspirone does not appear to cause dependence and shows virtually no withdrawal symptoms
- May have less severe side effects than benzodiazepines
- Buspirone generally lacks sexual dysfunction
- Buspirone may reduce sexual dysfunction associated with GAD and with serotonergic antidepressants
- Sedative effects may be more likely at doses above 20 mg/day
- May have less anxiolytic efficacy than benzodiazepines for some patients
- Buspirone is generally reserved as an augmenting agent to treat anxiety



Suggested Reading

Apter JT, Allen LA. Buspirone: future directions. *J Clin Psychopharmacol* 1999;19:86-93.

Mahmood I, Sahaiwalla C. Clinical pharmacokinetics and pharmacodynamics of buspirone, an anxiolytic drug. *Clin Pharmacokinet* 1999;36:277-87.

Pecknold JC. A risk-benefit assessment of buspirone in the treatment of anxiety disorders. *Drug Saf* 1997;16:118-32.

Sramek JJ, Hong WW, Hamid S, Nape B, Cutler NR. Meta-analysis of the safety and tolerability of two dose regimens of buspirone in patients with persistent anxiety. *Depress Anxiety* 1999;9:131-4.

THERAPEUTICS

Brands • Celexa

see index for additional brand names

Generic? Yes**Class**

- Neuroscience-based Nomenclature: serotonin reuptake inhibitor (S-RI)
- SSRI (selective serotonin reuptake inhibitor); often classified as an antidepressant, but it is not just an antidepressant

Commonly Prescribed for

(bold for FDA approved)

Depression

- Premenstrual dysphoric disorder (PMDD)
- Obsessive-compulsive disorder (OCD)
- Panic disorder
- Generalized anxiety disorder (GAD)
- Posttraumatic stress disorder (PTSD)
- Social anxiety disorder (social phobia)

**How the Drug Works**

- Boosts neurotransmitter serotonin
- Blocks serotonin reuptake pump (serotonin transporter)
- Desensitizes serotonin receptors, especially serotonin 1A autoreceptors
- Presumably increases serotonergic neurotransmission
- Citalopram also has mild antagonist actions at H1 histamine receptors
- Citalopram's inactive R enantiomer may interfere with the therapeutic actions of the active S enantiomer at serotonin reuptake pumps

How Long Until It Works

- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure

since symptoms can recur after medicine stopped

- Continue treatment until all symptoms are gone (remission) or significantly reduced (e.g., OCD, PTSD)
- Once symptoms are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders may also need to be indefinite

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating in depression)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some patients who have an initial response may relapse even though they continue treatment, sometimes called "poop-out"
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer

**Best Augmenting Combos for Partial Response or Treatment Resistance**

- Trazodone, especially for insomnia
- Bupropion, mirtazapine, reboxetine, or atomoxetine (add with caution and at lower doses since citalopram could theoretically raise atomoxetine levels); use combinations of antidepressants with caution as this may activate bipolar disorder and suicidal ideation
- Modafinil, especially for fatigue, sleepiness, and lack of concentration
- Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression, treatment-resistant depression, or treatment-resistant anxiety disorders

- Benzodiazepines
- If all else fails for anxiety disorders, consider gabapentin or tiagabine
- Hypnotics for insomnia
- Classically, lithium, buspirone, or thyroid hormone

Tests

- None for healthy individuals

SIDE EFFECTS

How Drug Causes Side Effects

- Theoretically due to increases in serotonin concentrations at serotonin receptors in parts of the brain and body other than those that cause therapeutic actions (e.g., unwanted actions of serotonin in sleep centers causing insomnia, unwanted actions of serotonin in the gut causing diarrhea, etc.)
- Increasing serotonin can cause diminished dopamine release and might contribute to emotional flattening, cognitive slowing, and apathy in some patients
- Most side effects are immediate but often go away with time, in contrast to most therapeutic effects which are delayed and are enhanced over time
- ✿ Citalopram's unique mild antihistamine properties may contribute to sedation and fatigue in some patients

Notable Side Effects

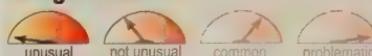
- Sexual dysfunction (dose-dependent; men: delayed ejaculation, erectile dysfunction; men and women: decreased sexual desire, anorgasmia)
- Gastrointestinal (decreased appetite, nausea, diarrhea, constipation, dry mouth)
- Mostly CNS (dose-dependent insomnia but also sedation, agitation, tremors, headache, dizziness)
- Activation (short-term; patients with diagnosed or undiagnosed bipolar or psychotic disorders may be more vulnerable to CNS-activating actions of SSRIs)
- Sweating (dose-dependent)
- Bruising and rare bleeding
- Rare hyponatremia (mostly in elderly patients and generally reversible on discontinuation of citalopram)
- SIADH (syndrome of inappropriate antidiuretic hormone secretion)



Life-Threatening or Dangerous Side Effects

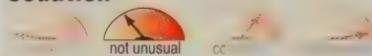
- Rare seizures
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Reported but not expected
- Citalopram has been associated with both weight gain and weight loss in various studies, but is relatively weight neutral overall

Sedation



- Occurs in significant minority

What to Do About Side Effects

- Wait
- Wait
- Wait
- Take in the morning if nighttime insomnia
- Take at night if daytime sedation
- In a few weeks, switch to another agent or add other drugs

Best Augmenting Agents for Side Effects

- Often best to try another SSRI or another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
- Trazodone or a hypnotic for insomnia
- Bupropion, sildenafil, vardenafil, or tadalafil for sexual dysfunction
- Bupropion for emotional flattening, cognitive slowing, or apathy
- Mirtazapine for insomnia, agitation, and gastrointestinal side effects
- Benzodiazepines for jitteriness and anxiety, especially at initiation of treatment and especially for anxious patients
- Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)

- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of citalopram

DOSING AND USE

Usual Dosage Range

- 20–40 mg/day

Dosage Forms

- Tablets 10 mg, 20 mg scored, 40 mg scored
- Orally disintegrating tablet 10 mg, 20 mg, 40 mg
- Capsule 10 mg, 20 mg, 40 mg

How to Dose

- Initial 20 mg/day; increase by 20 mg/day after 1 or more weeks; maximum 40 mg/day; single dose administration, morning or evening



Dosing Tips

- Citalopram should no longer be prescribed at doses greater than 40 mg/day because it can cause abnormal changes in the electrical activity of the heart
- Some controversy with FDA dosage limit of 40 mg/day, and higher doses may be prescribed by experts
- Tablets are scored, so to save costs, give 10 mg as half of 20-mg tablet or 20 mg as half of 40-mg tablet, since the tablets cost about the same in many markets
- Many patients respond better to 40 mg than to 20 mg
- Given once daily, any time of day when best tolerated by the individual
- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar

disorder and switch to a mood stabilizer or an atypical antipsychotic

Overdose

- Rare fatalities have been reported with citalopram overdose, both alone and in combination with other drugs
- Vomiting, sedation, heart rhythm disturbances, dizziness, sweating, nausea, tremor
- Rarely amnesia, confusion, coma, convulsions

Long-Term Use

- Safe

Habit Forming

- No

How to Stop

- Taper not usually necessary
- However, tapering to avoid potential withdrawal reactions generally prudent
- Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation
- If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly

Pharmacokinetics

- Parent drug has 23–45 hour half-life
- Weak inhibitor of CYP450 2D6
- Metabolized by CYP450 3A4 and 2C19



Drug Interactions

- Tramadol increases the risk of seizures in patients taking an antidepressant
- Can increase TCA levels; use with caution with TCAs
- Can cause a fatal “serotonin syndrome” when combined with MAOIs, so do not use with MAOIs or at least for 14 days after MAOIs are stopped
- Do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing citalopram
- May displace highly protein bound drugs (e.g., warfarin)
- Can rarely cause weakness, hyperreflexia, and incoordination when combined with

SPECIAL POPULATIONS

- sumatriptan or possibly other triptans, requiring careful monitoring of patient
- Possible increased risk of bleeding especially when combined with anticoagulants (e.g., warfarin, NSAIDs)
- NSAIDs may impair effectiveness of SSRIs
- Should not be dosed above 20 mg/day in patients taking a CYP450 2C19 inhibitor (e.g., cimetidine) due to risk of QT prolongation
- Via CYP450 2D6 inhibition, citalopram could theoretically interfere with the analgesic actions of codeine, and increase the plasma levels of some beta blockers and of atomoxetine
- Via CYP450 2D6 inhibition, citalopram could theoretically increase concentrations of thioridazine and cause dangerous cardiac arrhythmias



Other Warnings/ Precautions

- Use with caution in patients with history of seizures
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is taking an MAOI
- If patient is taking thioridazine or pimozide
- If there is a proven allergy to citalopram or escitalopram

Renal Impairment

- No dose adjustment for mild to moderate impairment
- Use cautiously in patients with severe impairment

Hepatic Impairment

- Should not be used at doses greater than 20 mg/day
- May need to dose cautiously at the lower end of the dose range in some patients for maximal tolerability

Cardiac Impairment

- May cause abnormal changes in the electrical activity of the heart at doses greater than 40 mg/day
- Treating depression with SSRIs in patients with acute angina or following myocardial infarction may reduce cardiac events and improve survival as well as mood

Elderly

- Doses greater than 20 mg/day should not be used in patients over age 60 years
- May need to dose at the lower end of the dose range in some patients for maximal tolerability
- Risk of SIADH with SSRIs is higher in the elderly
- Citalopram may be an especially well-tolerated SSRI in the elderly
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients

- Not specifically approved, but preliminary data suggest citalopram is safe and effective in children and adolescents with OCD and with depression



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester
- Nonetheless, continuous treatment during pregnancy may be necessary and has not been proven to be harmful to the fetus
- At delivery there may be more bleeding in the mother and transient irritability or sedation in the newborn
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients, this may mean continuing treatment during pregnancy
- Exposure to SSRIs early in pregnancy may be associated with increased risk of septal heart defects (absolute risk is small)
- SSRI use beyond the 20th week of pregnancy may be associated with increased risk of pulmonary hypertension in newborns, although this is not proven
- Exposure to SSRIs late in pregnancy may be associated with increased risk of gestational hypertension and preeclampsia
- Neonates exposed to SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding; reported symptoms are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome, and include respiratory distress, cyanosis,

apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying

Breast Feeding

- Some drug is found in mother's breast milk
- Trace amounts may be present in nursing children whose mothers are on citalopram
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients, this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Elderly patients
- Patients excessively activated or sedated by other SSRIs

Potential Disadvantages

- May require dosage titration to attain optimal efficacy
- Can be sedating in some patients

Primary Target Symptoms

- Depressed mood
- Anxiety
- Panic attacks, avoidant behavior, reexperiencing, hyperarousal
- Sleep disturbance, both insomnia and hypersomnia



Pearls

- May be more tolerable than some other antidepressants
- May have less sexual dysfunction than some other SSRIs

CITALOPRAM (continued)

- May be especially well tolerated in the elderly
- May be less well tolerated than escitalopram
- Documentation of efficacy in anxiety disorders is less comprehensive than for escitalopram and other SSRIs
- Can cause cognitive and affective "flattening"
- Some evidence suggests that citalopram treatment during only the luteal phase may be more effective than continuous treatment for patients with PMDD
- SSRIs may be less effective in women over 50, especially if they are not taking estrogen
- SSRIs may be useful for hot flushes in perimenopausal women
- Nonresponse to citalopram in elderly may require consideration of mild cognitive impairment or Alzheimer disease



Suggested Reading

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steps: a STAR*D report. Am J Psychiatry 2006;163(11):1905–17.

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THERAPEUTICS

Brands • Anafranil

see index for additional brand names

Generic? Yes



Class

- Neuroscience-based Nomenclature: serotonin reuptake inhibitor (SRI)
- Tricyclic antidepressant (TCA)
- Parent drug is a potent serotonin reuptake inhibitor
- Active metabolite is a potent norepinephrine/noradrenaline reuptake inhibitor

Commonly Prescribed for

(bold for FDA approved)

* Obsessive-compulsive disorder

- Depression
- Severe and treatment-resistant depression
- Cataplexy syndrome
- Anxiety
- Insomnia
- Neuropathic pain/chronic pain



How the Drug Works

- Boosts neurotransmitters serotonin and norepinephrine/noradrenaline
- Blocks serotonin reuptake pump (serotonin transporter), presumably increasing serotonergic neurotransmission
- Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing noradrenergic neurotransmission
- Presumably desensitizes both serotonin 1A receptors and beta adrenergic receptors
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, clomipramine can increase dopamine neurotransmission in this part of the brain

How Long Until It Works

- May have immediate effects in treating insomnia or anxiety
- Onset of therapeutic actions in depression usually not immediate, but often delayed 2 to 4 weeks
- Onset of therapeutic action in OCD can be delayed 6 to 12 weeks

- If it is not working for depression within 6 to 8 weeks, it may require a dosage increase or it may not work at all
- If it is not working for OCD within 12 weeks, it may not work at all
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment of depression is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Although the goal of treatment of OCD is also complete remission of symptoms, this may be less likely than in depression
- The goal of treatment of chronic neuropathic pain is to reduce symptoms as much as possible, especially in combination with other treatments
- Continue treatment of depression until all symptoms are gone (remission)
- Once symptoms of depression are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in OCD may also need to be indefinite, starting from the time of initial treatment
- Use in other anxiety disorders and chronic pain may also need to be indefinite, but long-term treatment is not well studied in these conditions

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy, especially behavioral therapy in OCD
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation

of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer



Best Augmenting Combos for Partial Response or Treatment Resistance

- Lithium, buspirone, hormone (for depression and OCD)
- For the expert: consider cautious addition of fluvoxamine for treatment-resistant OCD
- Thyroid hormone (for depression)
- Atypical antipsychotics (for OCD)

Tests

- Baseline ECG is recommended for patients over age 50

* Monitoring of plasma drug levels is potentially available at specialty laboratories for the expert

* Since tricyclic and tetracyclic antidepressants are frequently associated with weight gain, before starting treatment, weigh all patients and determine if the patient is already overweight (BMI 25.0–29.9) or obese (BMI \geq 30)

• Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–125 mg/dL), diabetes (fasting plasma glucose >126 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management

* Weight and BMI during treatment

* While giving a drug to a patient who has gained $>5\%$ of initial weight, consider evaluating for the presence of pre-diabetes, diabetes, or dyslipidemia, or consider switching to a different antidepressant

• EKGs may be useful for selected patients (e.g., those with personal or family history of QTc prolongation; cardiac arrhythmia; recent myocardial infarction; uncompensated heart failure; or taking agents that prolong QTc interval such as pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin, etc.)

• Patients at risk for electrolyte disturbances (e.g., patients on diuretic therapy)

should have baseline and periodic serum potassium and magnesium measurements

SIDE EFFECTS

How Drug Causes Side Effects

- Anticholinergic activity may explain sedative effects, dry mouth, constipation, and blurred vision
- Sedative effects and weight gain may be due to antihistamine properties
- Blockade of alpha adrenergic 1 receptors may explain dizziness, sedation, and hypotension
- Cardiac arrhythmias and seizures, especially in overdose, may be caused by blockade of ion channels

Notable Side Effects

- Blurred vision, constipation, urinary retention, increased appetite, dry mouth, nausea, diarrhea, heartburn, unusual taste in mouth, weight gain
- Fatigue, weakness, dizziness, sedation, headache, anxiety, nervousness, restlessness
- Sexual dysfunction, sweating



Life-Threatening or Dangerous Side Effects

- Paralytic ileus, hyperthermia (TCAs + anticholinergic agents)
- Lowered seizure threshold and rare seizures
- Orthostatic hypotension, sudden death, arrhythmias, tachycardia
- QTc prolongation
- Hepatic failure, extrapyramidal symptoms
- Increased intraocular pressure
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Many experience and/or can be significant in amount
- Can increase appetite and carbohydrate craving

Sedation



- Many experience and/or can be significant in amount
- Tolerance to sedative effect may develop with long-term use

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- Switch to an SSRI or newer antidepressant

Best Augmenting Agents for Side Effects

- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 100–200 mg/day

Dosage Forms

- Capsule 25 mg, 50 mg, 75 mg

How to Dose

- Initial 25 mg/day; increase over 2 weeks to 100 mg/day; maximum dose generally 250 mg/day



Dosing Tips

- If given in a single dose, should generally be administered at bedtime because of its sedative properties
- If given in split doses, largest dose should generally be given at bedtime because of its sedative properties
- If patients experience nightmares, split dose and do not give large dose at bedtime
- Patients treated for chronic pain may only require lower doses
- ✿ Patients treated for OCD may often require doses at the high end of the range (e.g., 200–250 mg/day)
- Risk of seizure increases with dose, especially with clomipramine at doses above 250 mg/day

✿ Dose of 300 mg may be associated with up to 7/1,000 incidence of seizures, a generally unacceptable risk

- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar disorder, and switch to a mood stabilizer or an atypical antipsychotic

Overdose

- Death may occur; convulsions, cardiac dysrhythmias, severe hypotension, CNS depression, coma, changes in EKG

Long-Term Use

- Limited data but appears to be efficacious and safe long-term

Habit Forming

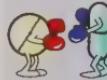
- No

How to Stop

- Taper to avoid withdrawal effects
- Even with gradual dose reduction some withdrawal symptoms may appear within the first 2 weeks
- Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation
- If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly

Pharmacokinetics

- Substrate for CYP450 2D6 and 1A2
- Metabolized to an active metabolite, desmethyl-clomipramine, a predominantly norepinephrine reuptake inhibitor, by demethylation via CYP450 1A2
- Inhibits CYP450 2D6
- Half-life approximately 17–28 hours
- Food does not affect absorption



Drug Interactions

- Tramadol increases the risk of seizures in patients taking TCAs
- Can cause a fatal “serotonin syndrome” when combined with MAOIs, so do not use with MAOI or at least for 14 days after MAOIs are stopped

- Do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing clomipramine
 - Use of TCAs with anticholinergic drugs may result in paralytic ileus or hyperthermia
 - Fluoxetine, paroxetine, bupropion, duloxetine, and other CYP450 2D6 inhibitors may increase TCA concentrations
 - Fluvoxamine, a CYP450 1A2 inhibitor, can decrease the conversion of clomipramine to desmethyl-clomipramine, and increase clomipramine plasma concentrations
 - Cimetidine may increase plasma concentrations of TCAs and cause anticholinergic symptoms
 - Phenothiazines or haloperidol may raise TCA blood concentrations
 - May alter effects of antihypertensive drugs
 - Use of TCAs with sympathomimetic agents may increase sympathetic activity
 - TCAs may inhibit hypotensive effects of clonidine
 - Methylphenidate may inhibit metabolism of TCAs
 - Activation and agitation, especially following switching or adding antidepressants, may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of clomipramine
- Because TCAs can prolong QTc interval, use with caution in patients who have hypokalemia and/or hypomagnesemia or who are taking drugs that can induce hypokalemia and/or magnesium (e.g., diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactide)
 - When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
 - Distribute the brochures provided by the FDA and the drug companies
 - Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
 - Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is taking an MAOI
- If patient is recovering from myocardial infarction
- If patient is taking agents capable of significantly prolonging QTc interval (e.g., pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin)
- If there is a history of QTc prolongation or cardiac arrhythmia, recent acute myocardial infarction, uncompensated heart failure
- If patient is taking drugs that inhibit TCA metabolism, including CYP450 2D6 inhibitors, except by an expert
- If there is reduced CYP450 2D6 function, such as patients who are poor 2D6 metabolizers, except by an expert and at low doses
- If there is a proven allergy to clomipramine



Other Warnings/ Precautions

- Add or initiate other antidepressants with caution for up to 2 weeks after discontinuing clomipramine
- Use with caution in patients with history of seizures, urinary retention, angle-closure glaucoma, hyperthyroidism
- TCAs can increase QTc interval, especially at toxic doses, which can be attained not only by overdose but also by combining with drugs that inhibit TCA metabolism via CYP450 2D6, potentially causing torsade de pointes-type arrhythmia or sudden death
- Because TCAs can prolong QTc interval, use with caution in patients who have bradycardia or who are taking drugs that can induce bradycardia (e.g., beta blockers, calcium channel blockers, clonidine, digitalis)

SPECIAL POPULATIONS

Renal Impairment

- Use with caution

Hepatic Impairment

- Use with caution

Cardiac Impairment

- Baseline ECG is recommended
- TCAs have been reported to cause arrhythmias, prolongation of conduction time, orthostatic hypotension, sinus tachycardia, and heart failure, especially in the diseased heart
- Myocardial infarction and stroke have been reported with TCAs
- TCAs produce QTc prolongation, which may be enhanced by the existence of bradycardia, hypokalemia, congenital or acquired long QTc interval, which should be evaluated prior to administering clomipramine
- Use with caution if treating concomitantly with a medication likely to produce prolonged bradycardia, hypokalemia, slowing of intracardiac conduction, or prolongation of the QTc interval
- Avoid TCAs in patients with a known history of QTc prolongation, recent acute myocardial infarction, and uncompensated heart failure
- TCAs may cause a sustained increase in heart rate in patients with ischemic heart disease and may worsen (decrease) heart rate variability, an independent risk of mortality in cardiac populations
- Since SSRIs may improve (increase) heart rate variability in patients following a myocardial infarct and may improve survival as well as mood in patients with acute angina or following a myocardial infarction, these are more appropriate agents for cardiac population than tricyclic/tetracyclic antidepressants
- Risk/benefit ratio may not justify use of TCAs in cardiac impairment

Elderly

- Baseline ECG is recommended for patients over age 50
- May be more sensitive to anticholinergic, cardiovascular, hypotensive, and sedative effects
- Dose may need to be lower than usual adult dose, at least initially
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Not recommended for use in children under age 10
- Several studies show lack of efficacy of TCAs for depression
- May be used to treat enuresis or hyperactive/impulsive behaviors
- Effective for OCD in children
- Some cases of sudden death have occurred in children taking TCAs
- Dose in children/adolescents should be titrated to a maximum of 100 mg/day or 3 mg/kg per day after 2 weeks, after which dose can then be titrated up to a maximum of 200 mg/day or 3 mg/kg per day



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Clomipramine crosses the placenta
- Adverse effects have been reported in infants whose mothers took a TCA (lethargy, withdrawal symptoms, fetal malformations)
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of

depression, worsening of OCD, maternal health, infant bonding) to the mother and child

- For many patients this may mean continuing treatment during pregnancy

Breast Feeding

- Some drug is found in mother's breast milk
- Recommended either to discontinue drug or bottle feed
- Immediate postpartum period is a high-risk time for depression and worsening of OCD, especially in women who have had prior depressive episodes or OCD symptoms, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence or exacerbation during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients with insomnia
- Severe or treatment-resistant depression
- Patients with comorbid OCD and depression
- Patients with cataplexy

Potential Disadvantages

- Pediatric and geriatric patients
- Patients concerned with weight gain
- Cardiac patients
- Patients with seizure disorders

Primary Target Symptoms

- Depressed mood
- Obsessive thoughts
- Compulsive behaviors



Pearls

- The only TCA with proven efficacy in OCD
- Normally, clomipramine (CMI), a potent serotonin reuptake blocker, at steady state is metabolized extensively to its

active metabolite desmethyl-clomipramine (de-CMI), a potent nonadrenaline reuptake blocker, by the enzyme CYP450 1A2

- Thus, at steady state, plasma drug activity is generally more noradrenergic (with higher de-CMI levels) than serotonergic (with lower parent CMI levels)
- Addition of the SSRI and CYP450 1A2 inhibitor fluvoxamine blocks this conversion and results in higher CMI levels than de-CMI levels
- For the expert only: addition of the SSRI fluvoxamine to CMI in treatment-resistant OCD can powerfully enhance serotonergic activity, not only due to the inherent additive pharmacodynamic serotonergic activity of fluvoxamine added to CMI, but also due to a favorable pharmacokinetic interaction inhibiting CYP450 1A2 and thus converting CMI's metabolism to a more powerful serotonergic portfolio of parent drug

- Recommended either to discontinue drug or bottle feed

- TCAs are no longer generally considered a first-line treatment option for depression because of their side effect profile
- TCAs continue to be useful for severe or treatment-resistant depression
- TCAs are often a first-line treatment option for chronic pain

- Unique among TCAs, clomipramine has a potentially fatal interaction with MAOIs in addition to the danger of hypertension characteristic of all MAOI-TCA combinations

- A potentially fatal serotonin syndrome with high fever, seizures, and coma, analogous to that caused by SSRIs and MAOIs, can occur with clomipramine and SSRIs, presumably due to clomipramine's potent serotonin reuptake blocking properties

- TCAs may aggravate psychotic symptoms
- Alcohol should be avoided because of additive CNS effects
- Underweight patients may be more susceptible to adverse cardiovascular effects
- Children, patients with inadequate hydration, and patients with cardiac disease may be more susceptible to TCA-induced cardiotoxicity than healthy adults

- Patients on TCAs should be aware that they may experience symptoms such as photosensitivity or blue-green urine
- SSRIs may be more effective than TCAs in women, and TCAs may be more effective than SSRIs in men
- Since tricyclic/tetracyclic antidepressants are substrates for CYP450 2D6, and 7% of the population (especially Caucasians) may have a genetic variant leading to reduced activity of 2D6, such patients may not safely tolerate normal doses of tricyclic/tetracyclic antidepressants and may require dose reduction
- Phenotypic testing may be necessary to detect this genetic variant prior to dosing with a tricyclic/tetracyclic antidepressant, especially in vulnerable populations such as children, elderly, cardiac populations, and those on concomitant medications
- Patients who seem to have extraordinarily severe side effects at normal or low doses may have this phenotypic CYP450 2D6 variant and require low doses or switching to another antidepressant not metabolized by 2D6



Suggested Reading

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Cox BJ, Swinson RP, Morrison B, Lee PS. Clomipramine, fluoxetine, and behavior therapy

in the treatment of obsessive-compulsive disorder: a meta-analysis. *J Behav Ther Exp Psychiatry* 1993;24:149–53.

Feinberg M. Clomipramine for obsessive-compulsive disorder. *Am Fam Physician* 1991; 43:1735–8.

THERAPEUTICS

Brands • Tercian*see index for additional brand names***Generic?** Not in the USA**Class**

- Conventional antipsychotic (neuroleptic, phenothiazine, dopamine 2 antagonist, serotonin dopamine antagonist)

Commonly Prescribed for*(bold for FDA approved)*

- Schizophrenia
- Anxiety associated with psychosis (short-term)
- Anxiety associated with nonpsychotic disorders, including mood disorders and personality disorders (short-term)
- Severe depression
- Bipolar disorder
- Other psychotic disorders
- Acute agitation/aggression (injection)
- Benzodiazepine withdrawal

**How the Drug Works**

- Blocks dopamine 2 receptors, reducing positive symptoms of psychosis
- Although classified as a conventional antipsychotic, cyamemazine is a potent serotonin 2A antagonist
- Affinity at a myriad of other neurotransmitter receptors may contribute to cyamemazine's efficacy
- Specifically, antagonist actions at 5HT2C receptors may contribute to notable anxiolytic effects in many patients
- 5HT2C antagonist actions may also contribute to antidepressant actions in severe depression and to improvement of cognitive and negative symptoms of schizophrenia in some patients

How Long Until It Works

- Psychotic symptoms can improve with high doses within 1 week, but it may take several weeks for full effect on behavior
- Anxiolytic actions can improve with low doses within 1 week, but it may take several days to weeks for full effect on behavior

If It Works

- High doses most often reduce positive symptoms in schizophrenia but do not eliminate them
- Low doses most often reduce anxiety symptoms in psychotic and nonpsychotic disorders
- Most schizophrenia patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third
- Continue treatment in schizophrenia until reaching a plateau of improvement
- After reaching a satisfactory plateau, continue treatment for at least a year, after first episode of psychosis in schizophrenia
- For second and subsequent episodes of psychosis in schizophrenia, treatment may need to be indefinite
- For symptomatic treatment of anxiety in psychotic and nonpsychotic disorders, treatment may also need to be indefinite while monitoring the risks versus the benefits of long-term treatment
- Reduces symptoms of acute psychotic mania but not proven as a mood stabilizer or as an effective maintenance treatment in bipolar disorder
- After reducing acute psychotic symptoms in mania, consider switching to a mood stabilizer and/or an atypical antipsychotic for long-term mood stabilization and maintenance

If It Doesn't Work

- For treatment of psychotic symptoms, consider trying one of the first-line atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, amisulpiride)
- Consider trying another conventional antipsychotic
- If 2 or more antipsychotic monotherapies do not work, consider clozapine
- For treatment of anxiety symptoms, consider adding a benzodiazepine or switching to a benzodiazepine

**Best Augmenting Combos for Partial Response or Treatment Resistance**

- Generally, best to switch to another agent
- Augmentation of conventional antipsychotics has not been systematically studied

- Addition of a mood-stabilizing anticonvulsant such as valproate, carbamazepine, or lamotrigine may be helpful in both schizophrenia and bipolar mania
- Augmentation with lithium in bipolar mania may be helpful
- Addition of a benzodiazepine, especially for short-term agitation
- Addition of antidepressants for severe depression

Tests

- Since conventional antipsychotics are frequently associated with weight gain, before starting treatment, weigh all patients and determine if the patient is already overweight (BMI 25.0–29.9) or obese (BMI ≥30)
- Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting glucose 100–125 mg/dL), diabetes (fasting plasma glucose >125 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management
- Monitor weight and BMI during treatment
- Consider monitoring fasting triglycerides monthly for several months in patients at high risk for metabolic complications and when initiating or switching antipsychotics
- While giving a drug to a patient who has gained >5% of initial weight, consider evaluating for the presence of pre-diabetes, diabetes, or dyslipidemia, or consider switching to a different antipsychotic
- Should check blood pressure in the elderly before starting and for the first few weeks of treatment
- Monitoring elevated prolactin levels of dubious clinical benefit
- Patients with low white blood cell count (WBC) or history of drug-induced leucopenia/neutropenia should have complete blood count (CBC) monitored frequently during the first few months and cyamemazine should be discontinued at the first sign of decline of WBC in the absence of other causative factors

SIDE EFFECTS

How Drug Causes Side Effects

- By blocking dopamine 2 receptors in the striatum, it can cause motor side effects at antipsychotic (high) doses
- Much lower propensity to cause motor side effects at low doses used to treat anxiety
- By blocking dopamine 2 receptors in the pituitary, it can cause elevations in prolactin, but unlike other conventional antipsychotics, prolactin elevations at low doses of cyamemazine are uncommon or transient
- By blocking dopamine 2 receptors excessively in the mesocortical and mesolimbic dopamine pathways, especially at high doses, it can cause worsening of negative and cognitive symptoms (neuroleptic-induced deficit syndrome)
- Anticholinergic actions, especially at high doses, may cause sedation, blurred vision, constipation, dry mouth
- Antihistamine actions may contribute to anxiolytic actions at low doses and to sedation and weight gain at high doses
- By blocking alpha 1 adrenergic receptors, cyamemazine can cause dizziness, sedation, and hypotension especially at high doses
- Mechanism of weight gain and any possible increased incidence of diabetes and dyslipidemia with conventional antipsychotics is unknown

Notable Side Effects

- Neuroleptic-induced deficit syndrome (unusual at low doses)
 - Akathisia
 - Extrapyramidal symptoms, parkinsonism, tardive dyskinesia (unusual at low doses)
 - Galactorrhea, amenorrhea (unusual at low doses)
 - Hypotension, tachycardia (unusual at low doses)
 - Dry mouth, constipation, vision disturbance, urinary retention
 - Sedation
 - Decreased sweating
 - Weight gain (may be unusual at low doses)
 - Sexual dysfunction
 - Metabolic effects, glucose tolerance



Life-Threatening or Dangerous Side Effects

- Rare neuroleptic malignant syndrome
- Rare seizures
- Rare jaundice, agranulocytosis
- Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis

Weight Gain



- Reported but not expected especially at low doses

Sedation



- Many experience and/or can be significant in amount, especially at high doses
- Sedation is usually dose-dependent and may not be experienced as sedation but as anxiolytic actions on anxiety and aggression at low doses where cyamemazine may function as an atypical antipsychotic (e.g., <300 mg/day; especially 25–100 mg/day)

What to Do About Side Effects

- Wait
- Wait
- Wait
- For motor symptoms, add an anticholinergic agent
- Reduce the dose
- For sedation, give at night
- Switch to an atypical antipsychotic
- Weight loss, exercise programs, and medical management for high BMIs, diabetes, dyslipidemia

Best Augmenting Agents for Side Effects

- Benztrapine or trihexyphenidyl for motor side effects
- Benzodiazepines may be helpful for akathisia
- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 50–300 mg at bedtime for treatment of psychosis
- 25–100 mg for anxiety; duration of treatment 4 weeks
- Children (ages 6 and older): 1–4 mg/kg per day
- Injection: 25–100 mg/day

Dosage Forms

- Tablet 25 mg, 100 mg
- Oral solution 40 mg/mL
- Injection 50 mg/5 mL

How to Dose

- Psychosis: usual maintenance dose 50–300 mg at bedtime; maximum dose 600 mg/day divided into 2 or 3 doses; after 2 weeks consider reducing to lowest effective dose
- Anxiety (adults): usual dose 25–100 mg/day; reduce dose if unacceptable sedation; maximum duration of treatment 4 weeks
- Anxiety (children): usual dose 1–4 mg/kg per day



Dosing Tips

- Has conventional antipsychotic properties at originally recommended high doses (300–600 mg/day)
- Binding studies, PET studies and clinical observations suggest that cyamemazine may be “atypical” with low motor side effects or prolactin elevations at low doses (below 300 mg/day)
- Clinical evidence suggests substantial anxiolytic benefits at 25–100 mg/day in many patients
- Clinical evidence suggests low EPS, little prolactin elevation yet demonstrable anxiolytic, anti-aggression and antidepressant actions at doses below 300 mg/day
- Robust antipsychotic actions on positive symptoms may require dosing above 300 mg/day
- Low doses up to 100 mg/day may be used to augment partial responders to other conventional or atypical antipsychotics, especially for anxiolytic actions
- Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³

Overdose

- Extrapyramidal symptoms, sedation, hypotension, coma, respiratory depression

Long-Term Use

- Some side effects may be irreversible (e.g., tardive dyskinesia)

Habit Forming

- No

How to Stop

- Slow down titration (over 6–8 weeks), especially when simultaneously beginning a new antipsychotic while switching (i.e., cross-titration)
- Rapid oral discontinuation of high doses of phenothiazines in psychotic patients may lead to rebound psychosis and worsening of symptoms
- If antiparkinsonian agents are being used, they should generally be continued for a few weeks after high-dose cyamemazine is discontinued

Pharmacokinetics

- Half-life 10 hours



Drug Interactions

- May decrease the effects of levodopa; contraindicated for use with dopamine agonists other than levodopa
- May increase the effects of antihypertensive drugs except for guanethidine, whose antihypertensive actions phenothiazines may antagonize
- May enhance QTc prolongation of other drugs capable of prolonging QTc interval
- Additive effects may occur if used with CNS depressants
- Anticholinergic effects may occur if used with atropine or related compounds
- Some patients taking a neuroleptic and lithium have developed an encephalopathic syndrome similar to neuroleptic malignant syndrome
- Epinephrine may lower blood pressure; diuretics and alcohol may increase risk of hypotension when administered with a phenothiazine



Other Warnings/ Precautions

- If signs of neuroleptic malignant syndrome develop, treatment should be immediately discontinued
- Use cautiously in patients with respiratory disorders
- Use cautiously in patients with alcohol withdrawal or convulsive disorders because phenothiazines can lower seizure threshold
- Do not use epinephrine in event of overdose as interaction with some pressor agents may lower blood pressure
- Avoid undue exposure to sunlight
- Avoid extreme heat exposure
- Use with caution in patients with respiratory disorders, glaucoma, or urinary retention
- Antiemetic effects of phenothiazines may mask signs of other disorders or overdose; suppression of cough reflex may cause asphyxia
- Observe for signs of ocular toxicity (corneal and lenticular deposits) as for other phenothiazines
- Use only with caution or at low doses, if at all, in Parkinson's disease or Lewy body dementia
- Because cyamemazine may dose-dependently prolong QTc interval, use with caution in patients who have bradycardia or who are taking drugs that can induce bradycardia (e.g., beta blockers, calcium channel blockers, clonidine, digitalis)
- Because cyamemazine may dose-dependently prolong QTc interval, use with caution in patients who have hyperkalemia and/or hypomagnesemia or who are taking drugs that can induce hypokalemia and/or magnesemia (e.g., diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactides)
- Cyamemazine can increase the QTc interval, potentially causing torsades de pointes-type arrhythmia or sudden death

Do Not Use

- If there is a history of QTc prolongation or cardiac arrhythmia, recent acute myocardial infarction, uncompensated heart failure
- If QTc interval greater than 450 msec or if taking an agent capable of prolonging the QTc interval

- If patient is taking sultopride
- If patient is in a comatose state or has CNS depression
- If there is the presence of blood dyscrasias, bone marrow depression, or liver disease
- If there is subcortical brain damage
- If patient has sensitivity to or intolerance of gluten (tablets contain gluten)
- If patient has congenital galactosemia, does not adequately absorb glucose/galactose, or has lactase deficit (tablets contain lactose)
- If patient is intolerant of fructose, does not adequately absorb glucose/galactose, or has sugar-isomaltase deficit (oral solution only; oral solution contains saccharose)
- If there is a proven allergy to cyamemazine
- If there is a known sensitivity to any phenothiazine

SPECIAL POPULATIONS

Renal Impairment

- Use with caution

Hepatic Impairment

- Use with caution

Cardiac Impairment

- Cardiovascular toxicity can occur, especially orthostatic hypotension

Elderly

- Elderly patients may be more susceptible to adverse effects
- Lower doses should be used and patient should be monitored closely
- Generally, doses above 100 mg/day are not recommended
- Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death compared to placebo, and also have an increased risk of cerebrovascular events



Children and Adolescents

- Sometimes used for severe behavioral disturbances in children ages 6 and older
- Oral solution is preferable to the other formulations



Pregnancy

- There is a risk of abnormal muscle movements and withdrawal symptoms in newborns whose mothers took an antipsychotic during the third trimester; symptoms may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty feeding
- Reports of extrapyramidal symptoms, jaundice, hyperreflexia, hyporeflexia in infants whose mothers took a phenothiazine during pregnancy
- Phenothiazines should only be used during pregnancy if clearly needed
- Psychotic symptoms may worsen during pregnancy and some form of treatment may be necessary
- Atypical antipsychotics may be preferable to phenothiazines or anticonvulsant mood stabilizers if treatment is required during pregnancy

Breast Feeding

- Unknown if cyamemazine is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- Recommended either to discontinue drug or bottle feed

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- For anxiety in patients with psychotic illnesses
- For anxiety in patients with nonpsychotic illnesses
- For severe depression

Potential Disadvantages

- Patients with tardive dyskinesia
- Children
- Elderly

Primary Target Symptoms

- Anxiety associated with psychosis
- Anxiety

- Aggression
- Agitation
- Positive symptoms of psychosis
- Severe depression



Pearls

- One of the most frequently prescribed antipsychotics in France, especially as a low-dose anxiolytic for psychotic patients
- ✿ Appears to have unique anxiolytic actions at low doses without rebound anxiety following discontinuation
- ✿ Low doses rarely associated with motor side effects or with prolactin elevation

✿ Recently discovered to be a serotonin dopamine antagonist with more potent binding of 5HT2A and 5HT2C receptors than D2 receptors (binding studies and PET scans)

- Low doses appear to saturate 5HT2A receptors in frontal cortex while not saturating D2 receptors in the striatum, accounting for apparent atypical antipsychotic and anxiolytic properties at low doses
- May be useful second-line therapy in facilitating benzodiazepine withdrawal for those patients in whom substitution with another benzodiazepine is not effective or is not appropriate



Suggested Reading

Lemoine P, Kermadi I, Garcia-Acosta S, Garay RP, Dib M. Double-blind, comparative study of cyamemazine vs. bromazepam in the benzodiazepine withdrawal syndrome. *Prog Neuropsychopharmacol Biol Psychiatry* 2006;30(1):131–7.

Hameg A, Bayle F, Nuss P, Dupuis P, et al. Affinity of cyamemazine, an anxiolytic antipsychotic drug, for human recombinant

dopamine vs. serotonin receptor subtypes. *Biochem Pharmacol* 2003;65(3):435–40.

Hode Y, Reimold M, Demazieres A, et al. A positron emission tomography (PET) study of cerebral dopamine D2 and serotonine 5-HT2A receptor occupancy in patients treated with cyamemazine (Tercian). *Psychopharmacology (Berl)* 2005;180(2):377–84.

THERAPEUTICS

Brands • Norpramin

see index for additional brand names

Generic? Yes**Class**

- Neuroscience-based Nomenclature: norepinephrine reuptake inhibitor (N-RI)
- Tricyclic antidepressant (TCA)
- Predominantly a norepinephrine/noradrenaline reuptake inhibitor

Commonly Prescribed for

(bold for FDA approved)

- **Depression**
- Anxiety
- Insomnia
- Neuropathic pain/chronic pain
- Treatment-resistant depression

**How the Drug Works**

- Boosts neurotransmitter norepinephrine/noradrenaline
- Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing noradrenergic neurotransmission
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, desipramine can thus increase dopamine neurotransmission in this part of the brain
- A more potent inhibitor of norepinephrine reuptake pump than serotonin reuptake pump (serotonin transporter)
- At high doses may also boost neurotransmitter serotonin and presumably increase serotonergic neurotransmission

How Long Until It Works

- May have immediate effects in treating insomnia or anxiety
- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment of depression is complete remission of current symptoms as well as prevention of future relapses
- The goal of treatment of chronic neuropathic pain is to reduce symptoms as much as possible, especially in combination with other treatments
- Treatment of depression most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Treatment of chronic neuropathic pain may reduce symptoms, but rarely eliminates them completely, and is not a cure since symptoms can recur after medicine is stopped
- Continue treatment of depression until all symptoms are gone (remission)
- Once symptoms of depression are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders and chronic pain may also need to be indefinite, but long-term treatment is not well studied in these conditions

If It Doesn't Work

- Many depressed patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other depressed patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent, or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer



Best Augmenting Combos for Partial Response or Treatment Resistance

- Lithium, buspirone, thyroid hormone (for depression)
- Gabapentin, tiagabine, other anticonvulsants, even opiates if done by experts while monitoring carefully in difficult cases (for chronic pain)

Tests

- Baseline ECG is recommended for patients over age 50
- Monitoring of plasma drug levels is available
- Since tricyclic and tetracyclic antidepressants are frequently associated with weight gain, before starting treatment, weigh all patients and determine if the patient is already overweight (BMI 25.0–29.9) or obese (BMI ≥30)
- Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–125 mg/dL), diabetes (fasting plasma glucose >126 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management
- Monitor weight and BMI during treatment
- While giving a drug to a patient who has gained >5% of initial weight, consider evaluating for the presence of pre-diabetes, diabetes, or dyslipidemia, or consider switching to a different antidepressant
- EKGs may be useful for selected patients (e.g., those with personal or family history of QTc prolongation; cardiac arrhythmia; recent myocardial infarction; uncompensated heart failure; or taking agents that prolong QTc interval such as pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin, etc.)
- Patients at risk for electrolyte disturbances (e.g., patients on diuretic therapy) should have baseline and periodic serum potassium and magnesium measurements

SIDE EFFECTS

How Drug Causes Side Effects

- Anticholinergic activity for desipramine may be somewhat less than for some other TCAs, yet can still explain the presence, if lower incidence, of sedative effects, dry mouth, constipation, and blurred vision
- Sedative effects and weight gain may be due to antihistamine properties
- Blockade of alpha adrenergic 1 receptors may explain dizziness, sedation, and hypotension
- Cardiac arrhythmias and seizures, especially in overdose, may be caused by blockade of ion channels

Notable Side Effects

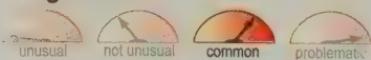
- Blurred vision, constipation, urinary retention, increased appetite, dry mouth, nausea, diarrhea, heartburn, unusual taste in mouth, weight gain
- Fatigue, weakness, dizziness, sedation, headache, anxiety, nervousness, restlessness
- Sexual dysfunction, sweating



Life-Threatening or Dangerous Side Effects

- Paralytic ileus, hyperthermia (TCAs + anticholinergic agents)
- Lowered seizure threshold and rare seizures
- Orthostatic hypotension, sudden death, arrhythmias, tachycardia
- QTc prolongation
- Hepatic failure, extrapyramidal symptoms
- Increased intraocular pressure
- Blood dyscrasias
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Many experience and/or can be significant in amount
- Can increase appetite and carbohydrate craving

Sedation



- Many experience and/or can be significant in amount
- Tolerance to sedative effects may develop with long-term use

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- Switch to an SSRI or newer antidepressant

Best Augmenting Agents for Side Effects

- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 100–200 mg/day (for depression)
- 50–150 mg/day (for chronic pain)

Dosage Forms

- Tablets 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg

How to Dose

- Initial 25 mg/day at bedtime; increase by 25 mg every 3–7 days
- 75 mg/day once daily or in divided doses; gradually increase dose to achieve desired therapeutic effect; maximum dose 300 mg/day



Dosing Tips

- If given in a single dose, should generally be administered at bedtime because of its sedative properties
- If given in split doses, largest dose should generally be given at bedtime because of its sedative properties
- If patients experience nightmares, split dose and do not give large dose at bedtime
- Patients treated for chronic pain may only require lower doses (e.g., 50–75 mg/day)
- Risk of seizure increases with dose
- Monitoring plasma levels of desipramine is recommended in patients who do not

respond to the usual dose or whose treatment is regarded as urgent

- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar disorder, and switch to a mood stabilizer or an atypical antipsychotic

Overdose

- Death may occur, and may be more likely than with other TCAs; convulsions, cardiac dysrhythmias, severe hypotension, CNS depression, coma, changes in EKG

Long-Term Use

- Safe

Habit Forming

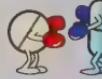
- No

How to Stop

- Taper to avoid withdrawal effects
- Even with gradual dose reduction some withdrawal symptoms may appear within the first 2 weeks
- Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation
- If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly

Pharmacokinetics

- Substrate for CYP450 2D6 and 1A2
- Is the active metabolite of imipramine, formed by demethylation via CYP450 1A2
- Half-life approximately 24 hours
- Food does not affect absorption



Drug Interactions

- Tramadol increases the risk of seizures in patients taking TCAs
- Use of TCAs with anticholinergic drugs may result in paralytic ileus or hyperthermia
- Fluoxetine, paroxetine, bupropion, duloxetine, and other CYP450 2D6 inhibitors may increase TCA concentrations
- Cimetidine may increase plasma concentrations of TCAs and cause anticholinergic symptoms
- Phenothiazines or haloperidol may raise TCA blood concentrations

- May alter effects of antihypertensive drugs; may inhibit hypotensive effects of clonidine
- Use of TCAs with sympathomimetic agents may increase sympathetic activity
- Methylphenidate may inhibit metabolism of TCAs
- Activation and agitation, especially following switching or adding antidepressants, may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of desipramine



Other Warnings/ Precautions

- Add or initiate other antidepressants with caution for up to 2 weeks after discontinuing desipramine
- Generally, do not use with MAOIs, including 14 days after MAOIs are stopped; do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing desipramine, but see Pearls
- Use with caution in patients with history of seizures, urinary retention, angle-closure glaucoma, hyperthyroidism
- Use caution when prescribing in patients with a family history of sudden death, cardiac dysrhythmias, and cardiac conduction disturbances
- Some patients may have seizures before cardiac dysrhythmias and death
- TCAs can increase QTc interval, especially at toxic doses, which can be attained not only by overdose but also by combining with drugs that inhibit TCA metabolism via CYP450 2D6, potentially causing torsade de pointes-type arrhythmia or sudden death
- Because TCAs can prolong QTc interval, use with caution in patients who have bradycardia or who are taking drugs that can induce bradycardia (e.g., beta blockers, calcium channel blockers, clonidine, digitalis)
- Because TCAs can prolong QTc interval, use with caution in patients who have hypokalemia and/or hypomagnesemia or who are taking drugs that can induce hypokalemia and/or magnesemia

- (e.g., diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactide)
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is recovering from myocardial infarction
- If patient is taking agents capable of significantly prolonging QTc interval (e.g., pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin)
- If there is a history of QTc prolongation or cardiac arrhythmia, recent acute myocardial infarction, uncompensated heart failure
- If patient is taking drugs that inhibit TCA metabolism, including CYP450 2D6 inhibitors, except by an expert
- If there is reduced CYP450 2D6 function, such as patients who are poor 2D6 metabolizers, except by an expert and at low doses
- If there is a proven allergy to desipramine, imipramine, or lofepramine

SPECIAL POPULATIONS

Renal Impairment

- Use with caution; may need to lower dose
- May need to monitor plasma levels

Hepatic Impairment

- Use with caution; may need to lower dose
- May need to monitor plasma levels

Cardiac Impairment

- Baseline ECG is recommended
- TCAs have been reported to cause arrhythmias, prolongation of conduction

- time, orthostatic hypotension, sinus tachycardia, and heart failure, especially in the diseased heart
- Myocardial infarction and stroke have been reported with TCAs
 - TCAs produce QTc prolongation, which may be enhanced by the existence of bradycardia, hypokalemia, congenital or acquired long QTc interval, which should be evaluated prior to administering desipramine
 - Use with caution if treating concomitantly with a medication likely to produce prolonged bradycardia, hypokalemia, slowing of intracardiac conduction, or prolongation of the QTc interval
 - Avoid TCAs in patients with a known history of QTc prolongation, recent acute myocardial infarction, and uncompensated heart failure
 - TCAs may cause a sustained increase in heart rate in patients with ischemic heart disease and may worsen (decrease) heart rate variability, an independent risk of mortality in cardiac populations
 - Since SSRIs may improve (increase) heart rate variability in patients following a myocardial infarct and may improve survival as well as mood in patients with acute angina or following a myocardial infarction, these are more appropriate agents for cardiac population than tricyclic/tetracyclic antidepressants

*** Risk/benefit ratio may not justify use of TCAs in cardiac impairment**

Elderly

- Baseline ECG is recommended for patients over age 50
- May be more sensitive to anticholinergic, cardiovascular, hypotensive, and sedative effects
- Initial dose 25–50 mg/day, raise to 100 mg/day; maximum 150 mg/day
- May be useful to monitor plasma levels in elderly patients
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against

the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart

- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Not recommended for use in children under age 12
- Several studies show lack of efficacy of TCAs for depression
- May be used to treat enuresis or hyperactive/impulsive behaviors
- May reduce tic symptoms
- Some cases of sudden death have occurred in children taking TCAs
- Adolescents: initial dose 25–50 mg/day, increase to 100 mg/day; maximum dose 150 mg/day
- May be useful to monitor plasma levels in children and adolescents



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Crosses the placenta
- Adverse effects have been reported in infants whose mothers took a TCA (lethargy, withdrawal symptoms, fetal malformations)
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy

Breast Feeding

- Some drug is found in mother's breast milk
- ✖ Recommended either to discontinue drug or bottle feed
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients this may mean continuing treatment during breast feeding

- Underweight patients may be more susceptible to adverse cardiovascular effects
- Children, patients with inadequate hydration, and patients with cardiac disease may be more susceptible to TCA-induced cardiotoxicity than healthy adults
- For the expert only: although generally prohibited, a heroic but potentially dangerous treatment for severely treatment-resistant patients is to give a tricyclic/tetracyclic antidepressant other than clomipramine simultaneously with an MAOI for patients who fail to respond to numerous other antidepressants
- If this option is elected, start the MAOI with the tricyclic/tetracyclic antidepressant simultaneously at low doses after appropriate drug washout, then alternately increase doses of these agents every few days to a week as tolerated
- Although very strict dietary and concomitant drug restrictions must be observed to prevent hypertensive crises and serotonin syndrome, the most common side effects of MAOI/tricyclic or tetracyclic combinations may be weight gain and orthostatic hypotension
- Patients on TCAs should be aware that they may experience symptoms such as photosensitivity or blue-green urine
- SSRIs may be more effective than TCAs in women, and TCAs may be more effective than SSRIs in men
- Not recommended for first-line use in children with ADHD because of the availability of safer treatments with better documented efficacy and because of desipramine's potential for sudden death in children

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients with insomnia
- Severe or treatment-resistant depression
- Patients for whom therapeutic drug monitoring is desirable

Potential Disadvantages

- Pediatric and geriatric patients
- Patients concerned with weight gain
- Cardiac patients

Primary Target Symptoms

- Depressed mood
- Chronic pain



Pearls

- TCAs are often a first-line treatment option for chronic pain
- TCAs are no longer generally considered a first-line option for depression because of their side effect profile
- TCAs continue to be useful for severe or treatment-resistant depression
- Noradrenergic reuptake inhibitors such as desipramine can be used as a second-line treatment for smoking cessation, cocaine dependence, and attention deficit disorder
- TCAs may aggravate psychotic symptoms
- Alcohol should be avoided because of additive CNS effects
- ✖ Desipramine is one of the few TCAs where monitoring of plasma drug levels has been well studied
- ✖ Fewer anticholinergic side effects than some other TCAs
- Since tricyclic/tetracyclic antidepressants are substrates for CYP450 2D6, and 7% of the population (especially Caucasians) may have a genetic variant leading to reduced activity of 2D6, such patients may not safely tolerate normal doses of tricyclic/tetracyclic antidepressants and may require dose reduction

- Phenotypic testing may be necessary to detect this genetic variant prior to dosing with a tricyclic/tetracyclic antidepressant, especially in vulnerable populations such as children, elderly, cardiac populations, and those on concomitant medications
- Patients who seem to have extraordinarily severe side effects at normal or low doses

may have this phenotypic CYP450 2D6 variant and require low doses or switching to another antidepressant not metabolized by 2D6



Suggested Reading

Anderson IM. Meta-analytical studies on new antidepressants. *Br Med Bull* 2001;57:161–78.

Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *J Aff Disorders* 2000;58:19–36.

Janowsky DS, Byerley B. Desipramine: an overview. *J Clin Psychiatry* 1984;45:3–9.

Levin FR, Lehman AF. Meta-analysis of desipramine as an adjunct in the treatment of cocaine addiction. *J Clin Psychopharmacol* 1991;11:374–8.

THERAPEUTICS

Brands • Pristiq

see index for additional brand names

Generic? No**Class**

- Neuroscience-based Nomenclature: serotonin norepinephrine reuptake inhibitor (SN-RI)
- SNRI (dual serotonin and norepinephrine reuptake inhibitor); often classified as an antidepressant, but it is not just an antidepressant

Commonly Prescribed for

(bold for FDA approved)

- Major depressive disorder
- Vasomotor symptoms
- Fibromyalgia
- Generalized anxiety disorder (GAD)
- Social anxiety disorder (social phobia)
- Panic disorder
- Posttraumatic stress disorder (PTSD)
- Premenstrual dysphoric disorder (PMDD)

**How the Drug Works**

- Boosts neurotransmitters serotonin, norepinephrine/noradrenaline, and dopamine
- Blocks serotonin reuptake pump (serotonin transporter), presumably increasing serotonergic neurotransmission
- Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing noradrenergic neurotransmission
- Desensitizes both serotonin 1A receptors and beta adrenergic receptors
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, desvenlafaxine can increase dopamine neurotransmission in this part of the brain

How Long Until It Works

- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6 or 8 weeks for depression, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of depressive symptoms
- Vasomotor symptoms in perimenopausal women with or without depression may improve within 1 week

If It Works

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Continue treatment until all symptoms are gone (remission) or significantly reduced
- Once symptoms are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some patients who have an initial response may relapse even though they continue treatment, sometimes called “poop-out”
- Consider increasing dose, switching to another agent, or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and switch to a mood stabilizer

**Best Augmenting Combos for Partial Response or Treatment Resistance**

- Mirtazapine (“California rocket fuel”; a potentially powerful dual serotonin and norepinephrine combination, but observe for activation of bipolar disorder and suicidal ideation)
- Bupropion, reboxetine, nortriptyline, desipramine, maprotiline, atomoxetine (all potentially powerful enhancers of noradrenergic action, but observe for activation of bipolar disorder and suicidal ideation)

- Modafinil, especially for fatigue, sleepiness, and lack of concentration
- Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression, or treatment-resistant depression
- Benzodiazepines
- If all else fails for anxiety disorders, consider gabapentin or tiagabine
- Hypnotics or trazodone for insomnia
- Classically, lithium, buspirone, or thyroid hormone

Tests

- Check blood pressure before initiating treatment and regularly during treatment

SIDE EFFECTS

How Drug Causes Side Effects

- Theoretically due to increases in serotonin and norepinephrine concentrations at receptors in parts of the brain and body other than those that cause therapeutic actions (e.g., unwanted actions of serotonin in sleep centers causing insomnia, unwanted actions of norepinephrine on acetylcholine release causing constipation and dry mouth, etc.)
- Most side effects are immediate but often go away with time

Notable Side Effects

- Most side effects increase with higher doses, at least transiently
- Insomnia, sedation, anxiety, dizziness
- Nausea, vomiting, constipation, decreased appetite
- Sexual dysfunction (abnormal ejaculation/orgasm, impotence)
- Sweating
- SIADH (syndrome of inappropriate antidiuretic hormone secretion)
- Hyponatremia
- Increase in blood pressure



Life-Threatening or Dangerous Side Effects

- Rare seizures
- Rare induction of hypomania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of

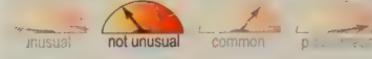
suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Reported but not expected

Sedation



- Occurs in significant minority
- May also be activating in some patients

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- In a few weeks, switch or add other drugs

Best Augmenting Agents for Side Effects

- Often best to try another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
- Trazodone or a hypnotic for insomnia
- Bupropion, sildenafil, vardenafil, or tadalafil for sexual dysfunction
- Benzodiazepines for jitteriness and anxiety, especially at initiation of treatment and especially for anxious patients
- Mirtazapine for insomnia, agitation, and gastrointestinal side effects
- Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of desvenlafaxine

DOSING AND USE

Usual Dosage Range

- Depression: 50 mg once daily

Dosage Forms

- Tablet (extended-release) 50 mg, 100 mg

How to Dose

- Initial dose 50 mg once daily; maximum recommended dose generally 100 mg once daily; doses up to 400 mg once daily have been shown to be effective but higher doses are associated with increased side effects



Dosing Tips

- Desvenlafaxine is the active metabolite O-desmethylvenlafaxine (ODV) of venlafaxine, and is formed as the result of CYP450 2D6
- More potent at the serotonin transporter (SERT) than at the norepinephrine transporter (NET), but has greater inhibition of NET relative to SERT compared to venlafaxine
- Nonresponders at lower doses may try higher doses to be assured of the benefits of dual SNRI action
- For vasomotor symptoms, current data suggest that a dose of 100 mg/day is effective
- Do not break or chew tablets, as this will alter controlled-release properties
- For some patients with severe problems discontinuing desvenlafaxine, it may be useful to add an SSRI with a long half-life, especially fluoxetine, prior to taper of desvenlafaxine. While maintaining fluoxetine dosing, first slowly taper desvenlafaxine and then taper fluoxetine
- Be sure to differentiate between reemergence of symptoms requiring reinstitution of treatment and withdrawal symptoms
- May dose up to 400 mg/day in patients who do not respond to lower doses, if tolerated

Overdose

- No fatalities have been reported as monotherapy; headache, vomiting, agitation, dizziness, nausea, constipation, diarrhea, dry mouth, paresthesia, tachycardia
- Desvenlafaxine is the active metabolite of venlafaxine; fatal toxicity index data from the UK suggest a higher rate of deaths

from overdose with venlafaxine than with SSRIs; it is unknown whether this is related to differences in patients who receive venlafaxine or to potential cardiovascular toxicity of venlafaxine

Long-Term Use

- See doctor regularly to monitor blood pressure

Habit Forming

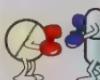
- No

How to Stop

- Taper to avoid withdrawal effects (dizziness, nausea, diarrhea, sweating, anxiety, irritability)
- Recommended taper schedule is to give a fully daily dose (50 mg) less frequently
- If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly

Pharmacokinetics

- Active metabolite of venlafaxine
- Half-life 9–13 hours
- Minimally metabolized by CYP450 3A4
- Food does not affect absorption



Drug Interactions

- Tramadol increases the risk of seizures in patients taking an antidepressant
- Can cause a fatal "serotonin syndrome" when combined with MAOIs, so do not use with MAOIs or for at least 14 days after MAOIs are stopped
- Do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing desvenlafaxine
- Can rarely cause weakness, hyperreflexia, and incoordination when combined with sumatriptan or possibly other triptans, requiring careful monitoring of patient
- Possible increased risk of bleeding, especially when combined with anticoagulants (e.g., warfarin, NSAIDs)
- NSAIDs may impair effectiveness of SSRIs
- Potent inhibitors of CYP450 3A4 may increase plasma levels of desvenlafaxine, but the clinical significance of this is unknown

- Few known adverse drug interactions
- False-positive urine immunoassay screening tests for phencyclidine (PCP) and amphetamine have been reported in patients taking desvenlafaxine, due to a lack of specificity of the screening tests. False-positive test results may be expected for several days following discontinuation of desvenlafaxine



Other Warnings/ Precautions

- Use with caution in patients with history of seizure
- Use with caution in patients with heart disease
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient has uncontrolled angle-closure glaucoma
- If patient is taking an MAOI
- If there is a proven allergy to desvenlafaxine or venlafaxine

SPECIAL POPULATIONS

Renal Impairment

- For moderate impairment, recommended dose is 50 mg/day
- For severe impairment, recommended dose is 50 mg every other day
- Patients on dialysis should not receive subsequent dose until dialysis is completed

Hepatic Impairment

- Doses greater than 100 mg/day not recommended

Cardiac Impairment

- Drug should be used with caution
- Hypertension should be controlled prior to initiation of desvenlafaxine and should be monitored regularly during treatment
- Desvenlafaxine has a dose-dependent effect on increasing blood pressure
- Desvenlafaxine is the active metabolite of venlafaxine, which is contraindicated in patients with heart disease in the UK
- Venlafaxine can block cardiac ion channels in vitro and worsens (i.e., reduces) heart rate variability in depression, perhaps due to norepinephrine reuptake inhibition

Elderly

- Some patients may tolerate lower doses better
- Risk of SIADH with SSRIs is higher in the elderly
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation

Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001

- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester
- Nonetheless, continuous treatment during pregnancy may be necessary and has not been proven to be harmful to the fetus
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy
- Exposure to SSRIs late in pregnancy may be associated with increased risk of gestational hypertension and preeclampsia
- Neonates exposed to SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding; reported symptoms are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome, and include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying

Breast Feeding

- Some drug is found in mother's breast milk
- Trace amounts may be present in nursing children whose mothers are on desvenlafaxine
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant

treatment versus nontreatment to both the infant and the mother

- For many patients, this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients with retarded depression
- Patients with atypical depression
- Patients with depression may have higher remission rates on SNRIs than on SSRIs
- Depressed patients with somatic symptoms, fatigue, and pain
- Depressed patients with vasomotor symptoms
- Patients who do not respond or remit on treatment with SSRIs

Potential Disadvantages

- Patients sensitive to nausea
- Patients with borderline or uncontrolled hypertension
- Patients with cardiac disease

Primary Target Symptoms

- Depressed mood
- Energy, motivation, and interest
- Sleep disturbance
- Physical symptoms
- Pain



Pearls

- Because desvenlafaxine is only minimally metabolized by CYP450 3A4 and is not metabolized at all by CYP450 2D6, as venlafaxine is, it should have more consistent plasma levels than venlafaxine
- In addition, although desvenlafaxine, like venlafaxine, is more potent at the serotonin transporter (SERT) than the norepinephrine transporter (NET), it has relatively greater actions on NET versus SERT than venlafaxine does at comparable doses
- The greater potency for NET may make it a preferable agent for conditions theoretically associated with targeting norepinephrine actions, such as vasomotor symptoms and fibromyalgia

- May be particularly helpful for hot flushes in perimenopausal women
- May be effective in patients who fail to respond to SSRIs
- May be used in combination with other antidepressants for treatment-refractory cases
- May be effective in a broad array of anxiety disorders and possibly adult ADHD, although it has not been studied in these conditions
- May be associated with higher depression remission rates than SSRIs
- Because of recent studies from the UK that suggest a higher rate of deaths from

overdose with venlafaxine than with SSRIs, and because of its potential to affect heart function, venlafaxine can only be prescribed in the UK by specialist doctors and is contraindicated there in patients with heart disease

- Overdose data are from fatal toxicity index studies, which do not take into account patient characteristics or whether drug use was first- or second-line
- Venlafaxine's toxicity in overdose is less than that for TCAs



Suggested Reading

Deecker DC, Beyer CE, Johnston G, et al. Desvenlafaxine succinate: a new serotonin and norepinephrine reuptake inhibitor. *J Pharmacol Exp Ther* 2006;318(2):657–65.

Lieberman DZ, Montgomery SA, Tourian KA, et al. A pooled analysis of two placebo-controlled trials of desvenlafaxine in major depressive disorder. *Int Clin Psychopharmacol* 2008;23(4):188–97.

Speroff L, Gass M, Constantine G. Efficacy and tolerability of desvenlafaxine succinate treatment for menopausal vasomotor symptoms: a randomized controlled trial. *Obstet Gynecol* 2008;111(1):77–87.

THERAPEUTICS

Brands • Prothiaden

see index for additional brand names
Generic? In UK

Class

- Neuroscience-based Nomenclature: serotonin, norepinephrine multi-modal (SN-MM)
- Tricyclic antidepressant (TCA)
- Serotonin and norepinephrine/noradrenaline reuptake inhibitor

Commonly Prescribed for
(bold for FDA approved)

- Major depressive disorder
- Anxiety
- Insomnia
- Neuropathic pain/chronic pain
- Treatment-resistant depression


How the Drug Works

- Boosts neurotransmitters serotonin and norepinephrine/noradrenaline
- Blocks serotonin reuptake pump (serotonin transporter), presumably increasing serotonergic neurotransmission
- Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing noradrenergic neurotransmission
- Presumably desensitizes both serotonin 1A receptors and beta adrenergic receptors
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, dothiepin can increase dopamine neurotransmission in this part of the brain

How Long Until It Works

- May have immediate effects in treating insomnia or anxiety
- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment of depression is complete remission of current symptoms as well as prevention of future relapses
- The goal of treatment of chronic neuropathic pain is to reduce symptoms as much as possible, especially in combination with other treatments
- Treatment of depression most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Treatment of chronic neuropathic pain may reduce symptoms, but rarely eliminates them completely, and is not a cure since symptoms can recur after medicine is stopped
- Continue treatment of depression until all symptoms are gone (remission)
- Once symptoms of depression are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders and chronic pain may also need to be indefinite, but long-term treatment is not well studied in these conditions

If It Doesn't Work

- Many depressed patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other depressed patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer



Best Augmenting Combos for Partial Response or Treatment Resistance

- Lithium, buspirone, thyroid hormone (for depression)
- Gabapentin, tiagabine, other anticonvulsants, even opiates if done by experts while monitoring carefully in difficult cases (for chronic pain)

Tests

- Baseline ECG is recommended for patients over age 50
- * Since tricyclic and tetracyclic antidepressants are frequently associated with weight gain, before starting treatment, weigh all patients and determine if the patient is already overweight (BMI 25.0–29.9) or obese (BMI ≥30)**
- Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–125 mg/dL), diabetes (fasting plasma glucose >126 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment including nutrition and weight management, physical activity counseling, smoking cessation, and medical management
- * Monitor weight and BMI during treatment**
- * While giving a drug to a patient who has gained >5% of initial weight, consider evaluating for the presence of pre-diabetes, diabetes, or dyslipidemia, or consider switching to a different antidepressant**
- EKGs may be useful for selected patients (e.g., those with personal or family history of QTc prolongation; cardiac arrhythmia; recent myocardial infarction; uncompensated heart failure; or taking agents that prolong QTc interval such as pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin, etc.)
- Patients at risk for electrolyte disturbances (e.g., patients on diuretic therapy) should have baseline and periodic serum potassium and magnesium measurements

SIDE EFFECTS

How Drug Causes Side Effects

- Anticholinergic activity may explain sedative effects, dry mouth, constipation, and blurred vision
- Sedative effects and weight gain may be due to antihistamine properties
- Blockade of alpha adrenergic 1 receptors may explain dizziness, sedation, and hypotension
- Cardiac arrhythmias and seizures, especially in overdose, may be caused by blockade of ion channels

Notable Side Effects

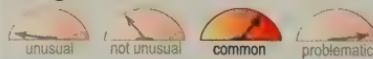
- Blurred vision, constipation, urinary retention, increased appetite, dry mouth, nausea, diarrhea, heartburn, unusual taste in mouth, weight gain
- Fatigue, weakness, dizziness, sedation, headache, anxiety, nervousness, restlessness
- Sexual dysfunction, sweating



Life-Threatening or Dangerous Side Effects

- Paralytic ileus, hyperthermia (TCAs + anticholinergic agents)
- Lowered seizure threshold and rare seizures
- Orthostatic hypotension, sudden death, arrhythmias, tachycardia
- QTc prolongation
- Hepatic failure, extrapyramidal symptoms
- Increased intraocular pressure
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Many experience and/or can be significant in amount
- Can increase appetite and carbohydrate craving

Sedation



- Many experience and/or can be significant in amount
- Tolerance to sedative effect may develop with long-term use

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- Switch to an SSRI or newer antidepressant

Best Augmenting Agents for Side Effects

- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 75–150 mg/day

Dosage Forms

- Capsule 25 mg
- Tablet 75 mg

How to Dose

- 75 mg/day once daily or in divided doses; gradually increase dose to achieve desired therapeutic effect; maximum dose 300 mg/day



Dosing Tips

- If given in a single dose, should generally be administered at bedtime because of its sedative properties
- If given in split doses, largest dose should generally be given at bedtime because of its sedative properties
- If patients experience nightmares, split dose and do not give large dose at bedtime
- Patients treated for chronic pain may only require lower doses
- Risk of seizure increases with dose
- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar

disorder, and switch to a mood stabilizer or an atypical antipsychotic

Overdose

- Death may occur; convulsions, cardiac dysrhythmias, severe hypotension, CNS depression, coma, changes in EKG

Long-Term Use

- Safe

Habit Forming

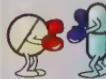
- No

How to Stop

- Taper to avoid withdrawal effects
- Even with gradual dose reduction some withdrawal symptoms may appear within the first 2 weeks
- Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation
- If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly

Pharmacokinetics

- Substrate for CYP450 2D6
- Half-life approximately 14–40 hours



Drug Interactions

- Tramadol increases the risk of seizures in patients taking TCAs
- Use of TCAs with anticholinergic drugs may result in paralytic ileus or hyperthermia
- Fluoxetine, paroxetine, bupropion, duloxetine, and other CYP450 2D6 inhibitors may increase TCA concentrations
- Cimetidine may increase plasma concentrations of TCAs and cause anticholinergic symptoms
- Phenothiazines or haloperidol may raise TCA blood concentrations
- May alter effects of antihypertensive drugs; may inhibit hypotensive effects of clonidine
- Use of TCAs with sympathomimetic agents may increase sympathetic activity
- Methylphenidate may inhibit metabolism of TCAs
- Activation and agitation, especially following switching or adding antidepressants, may represent the

induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of dothiepin



Other Warnings/ Precautions

- Add or initiate other antidepressants with caution for up to 2 weeks after discontinuing dothiepin
- Generally, do not use with MAOIs, including 14 days after MAOIs are stopped; do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing dothiepin, but see Pearls
- Use with caution in patients with history of seizures, urinary retention, angle-closure glaucoma, hyperthyroidism, and in patients recovering from myocardial infarction
- TCAs can increase QTc interval, especially at toxic doses, which can be attained not only by overdose but also by combining with drugs that inhibit TCA metabolism via CYP450 2D6, potentially causing torsade de pointes-type arrhythmia or sudden death
- Because TCAs can prolong QTc interval, use with caution in patients who have bradycardia or who are taking drugs that can induce bradycardia (e.g., beta blockers, calcium channel blockers, clonidine, digitalis)
- Because TCAs can prolong QTc interval, use with caution in patients who have hypokalemia and/or hypomagnesemia or who are taking drugs that can induce hypokalemia and/or magnesemia (e.g., diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactide)
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects

and advise them to report such symptoms immediately

- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is recovering from myocardial infarction
- If patient is taking agents capable of significantly prolonging QTc interval (e.g., pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin)
- If there is a history of QTc prolongation or cardiac arrhythmia, recent acute myocardial infarction, uncompensated heart failure
- If patient is taking drugs that inhibit TCA metabolism, including CYP450 2D6 inhibitors, except by an expert
- If there is reduced CYP450 2D6 function, such as patients who are poor 2D6 metabolizers, except by an expert and at low doses
- If there is a proven allergy to dothiepin

SPECIAL POPULATIONS

Renal Impairment

- Use with caution

Hepatic Impairment

- Use with caution

Cardiac Impairment

- Baseline ECG is recommended
- TCAs have been reported to cause arrhythmias, prolongation of conduction time, orthostatic hypotension, sinus tachycardia, and heart failure, especially in the diseased heart
- Myocardial infarction and stroke have been reported with TCAs
- TCAs produce QTc prolongation, which may be enhanced by the existence of bradycardia, hypokalemia, congenital or acquired long QTc interval, which should be evaluated prior to administering dothiepin
- Use with caution if treating concomitantly with a medication likely to produce prolonged bradycardia, hypokalemia, slowing of intracardiac conduction, or prolongation of the QTc interval

- Avoid TCAs in patients with a known history of QTc prolongation, recent acute myocardial infarction, and uncompensated heart failure
 - TCAs may cause a sustained increase in heart rate in patients with ischemic heart disease and may worsen (decrease) heart rate variability, an independent risk of mortality in cardiac populations
 - Since SSRIs may improve (increase) heart rate variability in patients following a myocardial infarct and may improve survival as well as mood in patients with acute angina or following a myocardial infarction, these are more appropriate agents for cardiac population than tricyclic/tetracyclic antidepressants
- * Risk/benefit ratio may not justify use of TCAs in cardiac impairment

Elderly

- Baseline ECG is recommended for patients over age 50
- May be more sensitive to anticholinergic, cardiovascular, hypotensive, and sedative effects
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Not recommended for use in children under age 18
- Several studies show lack of efficacy of TCAs for depression
- May be used to treat enuresis or hyperactive/impulsive behaviors
- Some cases of sudden death have occurred in children taking TCAs



Pregnancy

- Controlled studies have not been conducted in pregnant women
- Crosses the placenta
- Adverse effects have been reported in infants whose mothers took a TCA (lethargy, withdrawal symptoms, fetal malformations)
- Not generally recommended for use during pregnancy, especially during first trimester
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy

Breast Feeding

- Some drug is found in mother's breast milk
- * Recommended either to discontinue drug or bottle feed
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients with insomnia
- Severe or treatment-resistant depression
- Anxious depression

Potential Disadvantages

- Pediatric and geriatric patients
- Patients concerned with weight gain
- Cardiac patients

Primary Target Symptoms

- Depressed mood
- Chronic pain



Pearls

- Close structural similarity to amitriptyline
- TCAs are often a first-line treatment option for chronic pain
- TCAs are no longer generally considered a first-line option for depression because of their side effect profile
- TCAs continue to be useful for severe or treatment-resistant depression
- TCAs may aggravate psychotic symptoms
- Alcohol should be avoided because of additive CNS effects
- Underweight patients may be more susceptible to adverse cardiovascular effects
- Children, patients with inadequate hydration, and patients with cardiac disease may be more susceptible to TCA-induced cardiotoxicity than healthy adults
- For the expert only: a heroic treatment (but potentially dangerous) for severely treatment-resistant patients is to give simultaneously with MAOIs for patients who fail to respond to numerous other antidepressants, but generally recommend a different TCA than dothiepin for this use
- If this option is elected, start the MAOI with the tricyclic/tetracyclic antidepressant simultaneously at low doses after appropriate drug washout, then alternately increase doses of these agents every few days to a week as tolerated

- Although very strict dietary and concomitant drug restrictions must be observed to prevent hypertensive crises and serotonin syndrome, the most common side effects of MAOI and tricyclic/tetracyclic antidepressant combinations may be weight gain and orthostatic hypotension
- Patients on TCAs should be aware that they may experience symptoms such as photosensitivity or blue-green urine
- SSRIs may be more effective than TCAs in women, and TCAs may be more effective than SSRIs in men
- Since tricyclic/tetracyclic antidepressants are substrates for CYP450 2D6, and 7% of the population (especially Caucasians) may have a genetic variant leading to reduced activity of 2D6, such patients may not safely tolerate normal doses of tricyclic/tetracyclic antidepressants and may require dose reduction
- Phenotypic testing may be necessary to detect this genetic variant prior to dosing with a tricyclic/tetracyclic antidepressant, especially in vulnerable populations such as children, elderly, cardiac populations, and those on concomitant medications
- Patients who seem to have extraordinarily severe side effects at normal or low doses may have this phenotypic CYP450 2D6 variant and require low doses or switching to another antidepressant not metabolized by 2D6



Suggested Reading

Anderson IM. Meta-analytical studies on new antidepressants. *Br Med Bull* 2001; 57:161–78.

Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *J Aff Disorders* 2000;58:19–36.

Donovan S, Dearden L, Richardson L. The tolerability of dothiepin: a review of

clinical studies between 1963 and 1990 in over 13,000 depressed patients. *Prog Neuropsychopharmacol Biol Psychiatry* 1994; 18:1143–62.

Lancaster SG, Gonzalez JP. Dothiepin. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depressive illness. *Drugs* 1989;38:123–47.

THERAPEUTICS

Brands • Sinequan, Silenor
see index for additional brand names

Generic? Yes

**Class**

- Neuroscience-based Nomenclature: serotonin, norepinephrine multi-modal (SN-MM)
- Tricyclic antidepressant (TCA)
- Serotonin and norepinephrine/noradrenaline reuptake inhibitor
- Antihistamine

Commonly Prescribed for

(bold for FDA approved)

- **Psychoneurotic patient with depression and/or anxiety**
- Depression and/or anxiety associated with alcoholism
- Depression and/or anxiety associated with organic disease
- Psychotic depressive disorders with associated anxiety
- Involutional depression
- Manic-depressive disorder
- Insomnia (difficulty with sleep maintenance) (**Silenor only**)
- Pruritus/itching (topical)
- Dermatitis, atopic (topical)
- Lichen simplex chronicus (topical)
- Anxiety
- Neuropathic pain/chronic pain
- Treatment-resistant depression

**How the Drug Works**

At antidepressant doses:

- Boosts neurotransmitters serotonin and norepinephrine/noradrenaline
- Blocks serotonin reuptake pump (serotonin transporter), presumably increasing serotonergic neurotransmission
- Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing noradrenergic neurotransmission
- Presumably desensitizes both serotonin 1A receptors and beta adrenergic receptors
- Since dopamine is inactivated by norepinephrine reuptake in frontal

cortex, which largely lacks dopamine transporters, doxepin can thus increase dopamine neurotransmission in this part of the brain

- May be effective in treating skin conditions because of its strong antihistamine properties
- At hypnotic doses (3–6 mg/day):
- Selectively and potently blocks histamine 1 receptors, presumably decreasing wakefulness and thus promoting sleep

How Long Until It Works

- May have immediate effects in treating insomnia or anxiety
- Onset of therapeutic actions in depression is usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of depressive symptoms
- May also work long-term for insomnia (studied for up to 12 weeks)

If It Works

- The goal of treatment of depression is complete remission of current symptoms as well as prevention of future relapses
- The goal of treatment of insomnia is to improve quality of sleep, including effects on total wake time and number of nighttime awakenings.
- The goal of treatment of chronic neuropathic pain is to reduce symptoms as much as possible, especially in combination with other treatments
- Treatment of depression most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Treatment of chronic neuropathic pain may reduce symptoms, but rarely eliminates them completely, and is not a cure since symptoms can recur after medicine is stopped
- Continue treatment of depression until all symptoms are gone (remission)
- Once symptoms of depression are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite .

- Use in anxiety disorders, chronic pain, and skin conditions may also need to be indefinite, but long-term treatment is not well studied in these conditions

If It Doesn't Work

- Many depressed patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other depressed patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer
- If insomnia does not improve after 7–10 days, it may be a manifestation of a primary psychiatric or physical illness such as obstructive sleep apnea or restless leg syndrome, which requires independent evaluation



Best Augmenting Combos for Partial Response or Treatment Resistance

- Lithium, buspirone, thyroid hormone (for depression)
- Trazodone, GABAergic sedative hypnotics (for insomnia)
- Gabapentin, tiagabine, other anticonvulsants, even opiates if done by experts while monitoring carefully in difficult cases (for chronic pain)

Tests

- Baseline ECG is recommended for patients over age 50 (not for Silenor)
- Since tricyclic and tetracyclic antidepressants are frequently associated with weight gain, before starting treatment, weigh all patients and determine if the patient is already overweight (BMI 25.0–29.9) or obese (BMI ≥30)

- Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–125 mg/dL), diabetes (fasting plasma glucose >126 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment including nutrition and weight management, physical activity counseling, smoking cessation, and medical management
- Monitor weight and BMI during treatment
- While giving a drug to a patient who has gained >5% of initial weight, consider evaluating for the presence of pre-diabetes, diabetes, or dyslipidemia, or consider switching to a different antidepressant
- EKGs may be useful for selected patients (e.g., those with personal or family history of QTc prolongation; cardiac arrhythmia; recent myocardial infarction; uncompensated heart failure; or taking agents that prolong QTc interval such as pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin, etc.)
- Patients at risk for electrolyte disturbances (e.g., patients on diuretic therapy) should have baseline and periodic serum potassium and magnesium measurements

SIDE EFFECTS

How Drug Causes Side Effects

- At antidepressant doses, anticholinergic activity may explain sedative effects, dry mouth, constipation, and blurred vision
- Sedative effects and weight gain may be due to antihistamine properties
- At antidepressant doses, blockade of alpha adrenergic 1 receptors may explain dizziness, sedation, and hypotension
- Cardiac arrhythmias and seizures, especially in overdose, may be caused by blockade of ion channels

Notable Side Effects

Antidepressant Doses

- Blurred vision, constipation, urinary retention, increased appetite, dry mouth, nausea, diarrhea, heartburn, unusual taste in mouth, weight gain

- Fatigue, weakness, dizziness, sedation, headache, anxiety, nervousness, restlessness
- Sexual dysfunction, sweating
- Topical: burning, stinging, itching, or swelling at application site

Hypnotic Doses

- Few side effects at low doses (3–6 mg/day), the most common being somnolence/sedation



Life-Threatening or Dangerous Side Effects

- Paralytic ileus, hyperthermia (TCAs + anticholinergic agents)
- Lowered seizure threshold and rare seizures
- Orthostatic hypotension, sudden death, arrhythmias, tachycardia
- QTc prolongation
- Hepatic failure, extrapyramidal symptoms
- Increased intraocular pressure, increased psychotic symptoms
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Many experience and/or can be significant in amount (antidepressant doses)
- Can increase appetite and carbohydrate craving
- Weight gain is unusual at hypnotic doses

Sedation



- Many experience and/or can be significant in amount
- Tolerance to sedative effect may develop with long-term use
- Sedation is not unusual at hypnotic doses

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- Switch to an SSRI or newer antidepressant
- Switch to another hypnotic

Best Augmenting Agents for Side Effects

- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 75–150 mg/day for depression
- 3–6 mg at bedtime for insomnia

Dosage Forms

- Capsule 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg
- Solution 10 mg/mL
- Topical 5%
- Tablet 3 mg, 6 mg

How to Dose

- Initial 25 mg/day at bedtime; increase by 25 mg every 3–7 days
- 75 mg/day; increase gradually until desired efficacy is achieved; can be dosed once a day at bedtime or in divided doses; maximum dose 300 mg/day
- Topical: apply thin film 4 times a day (or every 3–4 hours while awake)
- Insomnia: 6 mg once daily, 30 minutes before bedtime; should not be taken within 3 hours of a meal; maximum dose 6 mg/day



Dosing Tips

- If given in a single antidepressant dose, should generally be administered at bedtime because of its sedative properties
- If given in split antidepressant doses, largest dose should generally be given at bedtime because of its sedative properties
- If patients experience nightmares, split antidepressant dose and do not give large dose at bedtime
- Patients treated for chronic pain may only require lower doses
- Patients treated for insomnia may benefit from doses of 3–6 mg at bedtime
- Liquid formulation should be diluted with water or juice, excluding grape juice
- 150-mg capsule available only for maintenance use, not initial therapy
- *** Topical administration is absorbed systematically and can cause the**

same systematic side effects as oral administration

- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar disorder, and switch to a mood stabilizer or an atypical antipsychotic

Overdose

- Death may occur; convulsions, cardiac dysrhythmias, severe hypotension, CNS depression, coma, changes in EKG

Long-Term Use

- Safe

Habit Forming

- No

How to Stop

- At antidepressant doses, taper to avoid withdrawal effects
- Even with gradual dose reduction some withdrawal symptoms may appear within the first 2 weeks
- Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation
- If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly
- Taper not necessary for low doses (3–6 mg/day); withdrawal effects generally not observed

Pharmacokinetics

- Substrate for CYP450 2D6
- Half-life approximately 8–24 hours



Drug Interactions

- Tramadol increases the risk of seizures in patients taking TCAs
- Use of TCAs with anticholinergic drugs may result in paralytic ileus or hyperthermia
- Fluoxetine, paroxetine, bupropion, duloxetine, and other CYP450 2D6 inhibitors may increase TCA concentrations
- Cimetidine may increase plasma concentrations of TCAs and cause anticholinergic symptoms

- Phenothiazines or haloperidol may raise TCA blood concentrations
- May alter effects of antihypertensive drugs; may inhibit hypotensive effects of clonidine
- Use with sympathomimetic agents may increase sympathetic activity
- Methylphenidate may inhibit metabolism of TCAs
- Most drug interactions may be less likely at low doses (1–6 mg/day) due to the lack of effects on receptors other than the histamine 1 receptors
- Activation and agitation, especially following switching or adding antidepressants, may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of doxepin



Other Warnings/ Precautions

- Add or initiate other antidepressants with caution for up to 2 weeks after discontinuing doxepin
- Generally, do not use with MAOIs, including 14 days after MAOIs are stopped; do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing doxepin, but see Pearls
- Use with caution in patients with history of seizures, urinary retention, angle-closure glaucoma, hyperthyroidism
- TCAs can increase QTc interval, especially at toxic doses, which can be attained not only by overdose but also by combining with drugs that inhibit TCA metabolism via CYP450 2D6, potentially causing torsade de pointes-type arrhythmia or sudden death
- Because TCAs can prolong QTc interval, use with caution in patients who have bradycardia or who are taking drugs that can induce bradycardia (e.g., beta blockers, calcium channel blockers, clonidine, digitalis)
- Because TCAs can prolong QTc interval, use with caution in patients who have hypokalemia and/or hypomagnesemia or who are taking drugs that can induce hypokalemia and/or magnesiumemia (e.g.,

diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactide)

- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is recovering from myocardial infarction
- If patient is taking agents capable of significantly prolonging QTc interval (e.g., pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin)
- If there is a history of QTc prolongation or cardiac arrhythmia, recent acute myocardial infarction, uncompensated heart failure
- If patient is taking drugs that inhibit TCA metabolism, including CYP450 2D6 inhibitors, except by an expert
- If there is reduced CYP450 2D6 function, such as patients who are poor 2D6 metabolizers, except by an expert and at low doses
- If patient has angle-closure glaucoma or severe urinary retention
- If there is a proven allergy to doxepin

SPECIAL POPULATIONS

Renal Impairment

- Use with caution

Hepatic Impairment

- Use with caution – may need lower than usual adult dose

Cardiac Impairment

- Baseline ECG is recommended (not for Silenor)
- TCAs have been reported to cause arrhythmias, prolongation of conduction

time, orthostatic hypotension, sinus tachycardia, and heart failure, especially in the diseased heart

- Myocardial infarction and stroke have been reported with TCAs
- TCAs produce QTc prolongation, which may be enhanced by the existence of bradycardia, hypokalemia, congenital or acquired long QTc interval, which should be evaluated prior to administering doxepin
- Use with caution if treating concomitantly with a medication likely to produce prolonged bradycardia, hypokalemia, slowing of intracardiac conduction, or prolongation of the QTc interval
- Avoid TCAs in patients with a known history of QTc prolongation, recent acute myocardial infarction, and uncompensated heart failure
- TCAs may cause a sustained increase in heart rate in patients with ischemic heart disease and may worsen (decrease) heart rate variability, an independent risk of mortality in cardiac populations
- Since SSRIs may improve (increase) heart rate variability in patients following a myocardial infarct and may improve survival as well as mood in patients with acute angina or following a myocardial infarction, these are more appropriate agents for cardiac population than tricyclic/tetracyclic antidepressants

★ Risk/benefit ratio may not justify use of TCAs in cardiac impairment

Elderly

- Baseline ECG is recommended for patients over age 50 (not for Silenor)
- May be more sensitive to anticholinergic, cardiovascular, hypotensive, and sedative effects
- Low-dose doxepin (3–6 mg/day) has been studied and found effective for insomnia in elderly patients; recommended dose is 3 mg/day
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against

- the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
 - Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
 - Not recommended for use in children under age 12
 - Several studies show lack of efficacy of TCAs for depression
 - May be used to treat enuresis or hyperactive/impulsive behaviors
 - Some cases of sudden death have occurred in children taking TCAs
 - Initial dose 25–50 mg/day; maximum 100 mg/day



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLL or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Crosses the placenta
- Adverse effects have been reported in infants whose mothers took a TCA (lethargy, withdrawal symptoms, fetal malformations)
- Not generally recommended for use during pregnancy, especially during first trimester
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy for depression

Breast Feeding

- Some drug is found in mother's breast milk
- Significant drug levels have been detected in some nursing infants
- ✖ Recommended either to discontinue drug or bottle feed
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients with insomnia
- Severe or treatment-resistant depression
- Patients with neurodermatitis and itching

Potential Disadvantages

- Pediatric and geriatric patients
- Patients concerned with weight gain
- Cardiac patients

Primary Target Symptoms

- Depressed mood
- Anxiety
- Disturbed sleep, energy
- Somatic symptoms
- Itching skin



Pearls

- ✖ Only TCA available in topical formulation
- ✖ Topical administration may reduce symptoms in patients with various neurodermatitis syndromes, especially itching
- Although low doses are specifically approved for sleep maintenance in insomnia they may also work for sleep onset in insomnia
- At low doses, one of the few hypnotics that is not a controlled substance, because it

- has no risk of dependence, withdrawal, or abuse
- At low doses, there is no tolerance to hypnotic actions seen
- At low doses, there is little or no weight gain
- At low doses doxepin is selective for the histamine 1 receptor and thus can improve sleep without causing side effects associated with other neurotransmitter systems
- In particular, low-dose doxepin does not appear to cause anticholinergic symptoms, memory impairment, or weight gain, nor is there evidence of tolerance, rebound insomnia, or withdrawal effects
- TCAs are often a first-line treatment option for chronic pain
- TCAs are no longer generally considered a first-line option for depression because of their side effect profile
- TCAs continue to be useful for severe or treatment-resistant depression
- TCAs may aggravate psychotic symptoms
- Alcohol should be avoided because of additive CNS effects
- Underweight patients may be more susceptible to adverse cardiovascular effects
- Children, patients with inadequate hydration, and patients with cardiac disease may be more susceptible to TCA-induced cardiotoxicity than healthy adults
- For the expert only: although generally prohibited, a heroic but potentially dangerous treatment for severely treatment-resistant patients is to give a tricyclic/tetracyclic antidepressant other than clomipramine simultaneously with an MAOI for patients who fail to respond to numerous other antidepressants

- If this option is elected, start the MAOI with the tricyclic/tetracyclic antidepressant simultaneously at low doses after appropriate drug washout, then alternately increase doses of these agents every few days to a week as tolerated
- Although very strict dietary and concomitant drug restrictions must be observed to prevent hypertensive crises and serotonin syndrome, the most common side effects of MAOI/tricyclic or tetracyclic combinations may be weight gain and orthostatic hypotension
- Patients on TCAs should be aware that they may experience symptoms such as photosensitivity or blue-green urine
- SSRIs may be more effective than TCAs in women, and TCAs may be more effective than SSRIs in men
- Since tricyclic/tetracyclic antidepressants are substrates for CYP450 2D6, and 7% of the population (especially Caucasians) may have a genetic variant leading to reduced activity of 2D6, such patients may not safely tolerate normal doses of tricyclic/tetracyclic antidepressants and may require dose reduction
- Phenotypic testing may be necessary to detect this genetic variant prior to dosing with a tricyclic/tetracyclic antidepressant, especially in vulnerable populations such as children, elderly, cardiac populations, and those on concomitant medications
- Patients who seem to have extraordinarily severe side effects at normal or low doses may have this phenotypic CYP450 2D6 variant and require low doses or switching to another antidepressant not metabolized by 2D6



Suggested Reading

- Anderson IM. Meta-analytical studies on new antidepressants. *Br Med Bull* 2001;57:161–78.
- Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *J Aff Disorders* 2000;58:19–36.
- Godfrey RG. A guide to the understanding and use of tricyclic antidepressants in the overall management of fibromyalgia and other chronic pain syndromes. *Arch Intern Med* 1996;156:1047–52.
- Roth T, Rogowski R, Hull S, et al. Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in adults with primary insomnia. *Sleep* 2007;30(11):1555–61.
- Singh H, Becker PM. Novel therapeutic usage of low-dose doxepin hydrochloride. *Expert Opin Investig Drugs* 2007;16(8):1295–305.
- Stahl SM. Selective histamine 1 antagonism: novel hypnotic and pharmacologic actions challenge classical notions of antihistamines. *CNS Spectrums* 2008;13(12):855–65.

THERAPEUTICS

Brands • Cymbalta
see index for additional brand names

Generic? Yes

**Class**

- Neuroscience-based Nomenclature: serotonin norepinephrine reuptake inhibitor (SN-RI)
- SNRI (dual serotonin and norepinephrine reuptake inhibitor); may be classified as an antidepressant, but it is not just an antidepressant

Commonly Prescribed for

(bold for FDA approved)

- Major depressive disorder
- Diabetic peripheral neuropathic pain (DPNP)
- Fibromyalgia
- Generalized anxiety disorder, acute and maintenance
- Chronic musculoskeletal pain
- Stress urinary incontinence
- Neuropathic pain/chronic pain
- Other anxiety disorders

**How the Drug Works**

- Boosts neurotransmitters serotonin, norepinephrine/noradrenaline, and dopamine
- Blocks serotonin reuptake pump (serotonin transporter), presumably increasing serotonergic neurotransmission
- Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing noradrenergic neurotransmission
- Presumably desensitizes both serotonin 1A receptors and beta adrenergic receptors
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, duloxetine can increase dopamine neurotransmission in this part of the brain
- Weakly blocks dopamine reuptake pump (dopamine transporter), and may increase dopamine neurotransmission

How Long Until It Works

- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks for depression

- If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all
- Can reduce neuropathic pain within a week, but onset can take longer
- May continue to work for many years to prevent relapse of depressive symptoms or prevent worsening of painful symptoms
- Vasomotor symptoms in perimenopausal women with or without depression may improve within 1 week

If It Works

- The goal of treatment of depression and anxiety disorders is complete remission of current symptoms as well as prevention of future relapses
- The goal of treatment of diabetic peripheral neuropathic pain and fibromyalgia and chronic neuropathic pain is to reduce symptoms as much as possible, especially in combination with other treatments
- Treatment of depression most often reduces or even eliminates symptoms, but is not a cure since symptoms can recur after medicine stopped
- Treatment of diabetic peripheral neuropathic pain, fibromyalgia, and chronic neuropathic pain may reduce symptoms, but rarely eliminates them completely, and is not a cure since symptoms can recur after medicine is stopped
- Continue treatment of depression and anxiety disorders until all symptoms are gone (remission)
- Once symptoms of depression are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders may also need to be indefinite
- Use in diabetic peripheral neuropathic pain, fibromyalgia, and chronic neuropathic pain may also need to be indefinite, but long-term treatment is not well studied in these conditions

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)

- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some depressed patients who have an initial response may relapse even though they continue treatment, sometimes called “poop-out”
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy for depression or biofeedback or hypnosis for pain
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Consider the presence of noncompliance and counsel the patient
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer



Best Augmenting Combos for Partial Response or Treatment Resistance

- ✿ Augmentation experience is limited compared to other antidepressants and treatments for neuropathic pain
- ✿ Adding other agents to duloxetine for treating depression could follow the same practice for augmenting SSRIs or other SNRIs if done by experts while monitoring carefully in difficult cases
- Although no controlled studies and little clinical experience, adding other agents for treating diabetic peripheral neuropathic pain and fibromyalgia and neuropathic pain could theoretically include gabapentin, pregabalin, and tiagabine, if done by experts while monitoring carefully in difficult cases
- Mirtazapine (“California rocket fuel” for depression; a potentially powerful dual serotonin and norepinephrine combination, but observe for activation of bipolar disorder and suicidal ideation)
- Bupropion, reboxetine, nortriptyline, desipramine, maprotiline, atomoxetine (all potentially powerful enhancers of noradrenergic action for depression, but observe for activation of bipolar disorder and suicidal ideation)
- Modafinil, especially for fatigue, sleepiness, and lack of concentration

- Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression, or treatment-resistant depression
- Benzodiazepines
- If all else fails for anxiety disorders, consider gabapentin, pregabalin, or tiagabine
- Hypnotics or trazodone for insomnia
- Classically, lithium, buspirone, or thyroid hormone for depression

Tests

- Check blood pressure before initiating treatment and regularly during treatment

SIDE EFFECTS

How Drug Causes Side Effects

- Theoretically due to increases in serotonin and norepinephrine concentrations at receptors in parts of the brain and body other than those that cause therapeutic actions (e.g., unwanted actions of serotonin in sleep centers causing insomnia, unwanted actions of norepinephrine on acetylcholine release causing decreased appetite, increased blood pressure, urinary retention, etc.)
- Most side effects are immediate but often go away with time

Notable Side Effects

- Nausea, diarrhea, decreased appetite, dry mouth, constipation (dose-dependent)
- Insomnia, sedation, dizziness
- Sexual dysfunction (men: abnormal ejaculation/orgasm, impotence, decreased libido; women: abnormal orgasm)
- Sweating
- Increase in blood pressure (up to 2 mm Hg)
- Urinary retention



Life-Threatening or Dangerous Side Effects

- Rare seizures
- Rare induction of hypomania
- Rare activation of suicidal ideation, suicide attempts, and completed suicide
- Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24

Weight Gain

- Reported but not expected

Sedation

- Occurs in significant minority
- May also be activating in some patients

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- In a few weeks, switch or add other drugs

Best Augmenting Agents for Side Effects

- For urinary hesitancy, give an alpha 1 blocker such as tamsulosin
- Often best to try another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
- Trazodone or a hypnotic for insomnia
- Bupropion, sildenafil, vardenafil, or tadalafil for sexual dysfunction
- Benzodiazepines for jitteriness and anxiety, especially at initiation of treatment and especially for anxious patients
- Mirtazapine for insomnia, agitation, and gastrointestinal side effects
- Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of duloxetine

DOSING AND USE**Usual Dosage Range**

- 40–60 mg/day in 1–2 doses for depression
- 60 mg once daily for diabetic peripheral neuropathic pain and fibromyalgia
- 60 mg once daily for generalized anxiety disorder
- 40 mg twice daily for stress urinary incontinence

Dosage Forms

- Capsule 20 mg, 30 mg, 60 mg

How to Dose

- For depression, initial 40 mg/day in 2 doses; can increase to 60 mg/day in 1–2 doses if necessary; maximum dose generally 120 mg/day
- For neuropathic pain and fibromyalgia initial 30 mg once daily; increase to 60 mg once daily after 1 week; maximum dose generally 60 mg/day
- For generalized anxiety, initial 60 mg once daily; maximum dose generally 120 mg/day

**Dosing Tips**

- Studies have not demonstrated increased efficacy beyond 60 mg/day
- Some patients may require up to or more than 120 mg/day, but clinical experience is quite limited with high dosing
- In relapse prevention studies in depression, a significant percentage of patients who relapsed on 60 mg/day responded and remitted when the dose was increased to 120 mg/day
- In neuropathic pain and fibromyalgia doses above 60 mg/day have been associated with increased side effects without an increase in efficacy
- Some studies suggest that both serotonin and norepinephrine reuptake blockade are present at 40–60 mg/day
- Do not chew or crush and do not sprinkle on food or mix with food, but rather always swallow whole to avoid affecting enteric coating
- Some patients may require dosing above 120 mg/day in 2 divided doses, but this should be done with caution and by experts

Overdose

- Rare fatalities have been reported; serotonin syndrome, sedation, vomiting, seizures, coma, change in blood pressure

Long-Term Use

- Blood pressure should be monitored regularly

Habit Forming

- No

How to Stop

- Taper to avoid withdrawal effects (dizziness, nausea, vomiting, headache, paresthesias, irritability)
- Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation
- If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly

Pharmacokinetics

- Elimination half-life approximately 12 hours
- Metabolized mainly by CYP450 2D6 and CYP450 1A2
- Inhibitor of CYP450 2D6 (probably clinically significant) and CYP450 1A2 (probably not clinically significant)
- Absorption may be delayed by up to 3 hours and clearance may be increased by one-third after an evening dose as compared to a morning dose
- Food does not affect absorption



Drug Interactions

- Can increase TCA levels; use with caution with TCAs or when switching from a TCA to duloxetine
- Can cause a fatal "serotonin syndrome" when combined with MAOIs, so do not use with MAOIs or for at least 14 days after MAOIs are stopped
- Possible increased risk of bleeding, especially when combined with anticoagulants (e.g., warfarin, NSAIDs)
- Do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing duloxetine
- Inhibitors of CYP450 1A2, such as fluvoxamine, increase plasma levels of

duloxetine and may require a dosage reduction of duloxetine

- Cigarette smoking induces CYP450 1A2 and may reduce plasma levels of duloxetine, but dosage modifications are not recommended for smokers

- Inhibitors of CYP450 2D6, such as paroxetine, fluoxetine, and quinidine, may increase plasma levels of duloxetine and require a dosage reduction of duloxetine

- Via CYP450 1A2 inhibition, duloxetine could theoretically reduce clearance of theophylline and clozapine; however, studies of coadministration with theophylline did not demonstrate significant effects of duloxetine on theophylline pharmacokinetics

- Via CYP450 2D6 inhibition, duloxetine could theoretically interfere with the analgesic actions of codeine, and increase the plasma levels of some beta blockers and of atomoxetine

- Via CYP450 2D6 inhibition, duloxetine could theoretically increase concentrations of thioridazine and cause dangerous cardiac arrhythmias



Other Warnings/ Precautions

- Use with caution in patients with history of seizures
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- Rare reports of hepatotoxicity; although causality has not been established, duloxetine should be discontinued in patients who develop jaundice or other evidence of significant liver dysfunction
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

- Duloxetine may increase blood pressure, so blood pressure should be monitored during treatment

Do Not Use

- If patient has uncontrolled angle-closure glaucoma
- If patient has substantial alcohol use
- If patient is taking an MAOI
- If patient is taking thioridazine
- If there is a proven allergy to duloxetine

SPECIAL POPULATIONS

Renal Impairment

- Dose adjustment generally not necessary for mild to moderate impairment
- Not recommended for use in patients with end-stage renal disease (requiring dialysis) or severe renal impairment

Hepatic Impairment

- Not to be administered to patients with any hepatic insufficiency
- Not recommended for use in patients with substantial alcohol use
- Increased risk of elevation of serum transaminase levels

Cardiac Impairment

- Drug should be used with caution
- Duloxetine may raise blood pressure

Elderly

- Some patients may tolerate lower doses better
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents

or guardians of this risk so they can help observe child or adolescent patients

- Not studied, but can be used by experts



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester
- Nonetheless, continuous treatment during pregnancy may be necessary and has not been proven to be harmful to the fetus
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy
- Neonates exposed to SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding; reported symptoms are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome, and include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying

Breast Feeding

- Some drug is found in mother's breast milk
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes,

so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period

- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients, this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients with physical symptoms of depression
- Patients with retarded depression
- Patients with atypical depression
- Patients with comorbid anxiety
- Patients with depression may have higher remission rates on SNRIs than on SSRIs
- Depressed patients with somatic symptoms, fatigue, and pain
- Patients who do not respond or do not remit on treatment with SSRIs

Potential Disadvantages

- Patients with urologic disorders, prostate disorders (e.g., older men)
- Patients sensitive to nausea

Primary Target Symptoms

- Depressed mood
- Energy, motivation, and interest
- Sleep disturbance

- Anxiety
- Physical symptoms
- Pain



Pearls

- Duloxetine has well-documented efficacy for the painful physical symptoms of depression
- Duloxetine has only somewhat greater potency for serotonin reuptake blockade than for norepinephrine reuptake blockade, but this is of unclear clinical significance as a differentiator from other SNRIs
- No head-to-head studies, but may have less hypertension than venlafaxine XR
- Powerful pro-noradrenergic actions may occur at doses greater than 60 mg/day
- Not well studied in ADHD, but may be effective
- Approved in many countries for stress urinary incontinence
- Patients may have higher remission rate for depression on SNRIs than on SSRIs
- Add or switch to or from pro-noradrenergic agents (e.g., atomoxetine, reboxetine, other SNRIs, mirtazapine, maprotiline, nortriptyline, desipramine, bupropion) with caution
- Add or switch to or from CYP450 2D6 substrates with caution (e.g., atomoxetine, maprotiline, nortriptyline, desipramine)
- Mechanism of action as SNRI suggests it may be effective in some patients who fail to respond to SSRIs



Suggested Reading

Arnold LM, Pritchett YL, D'Souza DN, et al. Duloxetine for the treatment of fibromyalgia in women: pooled results from two randomized, placebo-controlled trials. *J Womens Health (Larchmt)* 2007;16(8):1145–56.

Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG, et al. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors. *Neuropsychopharmacology* 2001;25(6):871–80.

Hartford J, Kornstein S, Liebowitz M, et al. Duloxetine as an SNRI treatment for

generalized anxiety disorder: results from placebo and active-controlled trial. *Int Clin Psychopharmacol* 2007;22(3):167–74.

Muller N, Schennach R, Riedel M, Moller HJ. Duloxetine in the treatment of major psychiatric and neuropathic disorders. *Expert Rev Neurother* 2008;8(4):527–36.

Zinner NR. Duloxetine: a serotonin-noradrenaline re-uptake inhibitor for the treatment of stress urinary incontinence. *Expert Opin Investig Drugs* 2003;12(9):1559–66.

THERAPEUTICS

Brands

- Lexapro
- see index for additional brand names

Generic?

Yes



Class

- Neuroscience-based Nomenclature: serotonin reuptake inhibitor (S-RI)
- SSRI (selective serotonin reuptake inhibitor); often classified as an antidepressant, but it is not just an antidepressant

Commonly Prescribed for

(bold for FDA approved)

- Major depressive disorder (ages 12 and older)**
- Generalized anxiety disorder (GAD)**
- Panic disorder
- Obsessive-compulsive disorder (OCD)
- Posttraumatic stress disorder (PTSD)
- Social anxiety disorder (social phobia)
- Premenstrual dysphoric disorder (PMDD)



How the Drug Works

- Boosts neurotransmitter serotonin
- Blocks serotonin reuptake pump (serotonin transporter)
- Desensitizes serotonin receptors, especially serotonin 1A autoreceptors
- Presumably increases serotonergic neurotransmission

How Long Until It Works

- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Continue treatment until all symptoms are gone (remission) or significantly reduced (e.g., OCD, PTSD)

- Once symptoms gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders may also need to be indefinite

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating in depression)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some patients who have an initial response may relapse even though they continue treatment, sometimes called "poop-out"
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer



Best Augmenting Combos for Partial Response or Treatment Resistance

- Trazodone, especially for insomnia
- Bupropion, mirtazapine, reboxetine, or atomoxetine (use combinations of antidepressants with caution as this may activate bipolar disorder and suicidal ideation)
- Modafinil, especially for fatigue, sleepiness, and lack of concentration
- Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression, treatment-resistant depression, or treatment-resistant anxiety disorders
- Benzodiazepines
- If all else fails for anxiety disorders, consider gabapentin or tiagabine
- Hypnotics for insomnia
- Classically, lithium, buspirone, or thyroid hormone

Tests

- None for healthy individuals

SIDE EFFECTS**How Drug Causes Side Effects**

- Theoretically due to increases in serotonin concentrations at serotonin receptors in parts of the brain and body other than those that cause therapeutic actions (e.g., unwanted actions of serotonin in sleep centers causing insomnia, unwanted actions of serotonin in the gut causing diarrhea, etc.)
- Increasing serotonin can cause diminished dopamine release and might contribute to emotional flattening, cognitive slowing, and apathy in some patients
- Most side effects are immediate but often go away with time, in contrast to most therapeutic effects which are delayed and are enhanced over time

* As escitalopram has no known important secondary pharmacologic properties, its side effects are presumably all mediated by its serotonin reuptake blockade

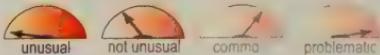
Notable Side Effects

- Sexual dysfunction (men: delayed ejaculation, erectile dysfunction; men and women: decreased sexual desire, anorgasmia)
- Gastrointestinal (decreased appetite, nausea, diarrhea, constipation, dry mouth)
- Mostly central nervous system (insomnia but also sedation, agitation, tremors, headache, dizziness)
- Note: patients with diagnosed or undiagnosed bipolar or psychotic disorders may be more vulnerable to CNS-activating actions of SSRIs
- Autonomic (sweating)
- Bruising and rare bleeding
- Rare hyponatremia (mostly in elderly patients and generally reversible on discontinuation of escitalopram)
- SIADH (syndrome of inappropriate antidiuretic hormone secretion)

**Life-Threatening or Dangerous Side Effects**

- Rare seizures
- Rare induction of mania

- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain

- Reported but not expected

Sedation

- Reported but not expected

What to Do About Side Effects

- Wait
- Wait
- Wait
- In a few weeks, switch to another agent or add other drugs

Best Augmenting Agents for Side Effects

- Often best to try another SSRI or another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
- Trazodone or a hypnotic for insomnia
- Bupropion, sildenafil, vardenafil, or tadalafil for sexual dysfunction
- Bupropion for emotional flattening, cognitive slowing, or apathy
- Mirtazapine for insomnia, agitation, and gastrointestinal side effects
- Benzodiazepines for jitteriness and anxiety, especially at initiation of treatment and especially for anxious patients
- Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of escitalopram

DOSING AND USE

Usual Dosage Range

- 10–20 mg/day

Dosage Forms

- Tablets 5 mg, 10 mg (scored), 20 mg (scored)
- Capsule 5 mg, 10 mg, 20 mg
- Oral solution 5 mg/5 mL

How to Dose

- Initial 10 mg/day; increase to 20 mg/day if necessary; single dose administration, morning or evening



Dosing Tips

- Given once daily, any time of day tolerated
- 10 mg of escitalopram may be comparable in efficacy to 40 mg of citalopram with fewer side effects
- Thus, give an adequate trial of 10 mg prior to giving 20 mg
- Some patients require dosing with 30 or 40 mg
- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar disorder and switch to a mood stabilizer or an atypical antipsychotic

Overdose

- Few reports of escitalopram overdose, but probably similar to citalopram overdose
- Rare fatalities have been reported in citalopram overdose, both in combination with other drugs and alone
- Symptoms associated with citalopram overdose include vomiting, sedation, heart rhythm disturbances, dizziness, sweating, nausea, tremor, and rarely amnesia, confusion, coma, convulsions

Long-Term Use

- Safe

Habit Forming

- No

How to Stop

- Taper not usually necessary
- However, tapering to avoid potential withdrawal reactions generally prudent

- Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation
- If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly

Pharmacokinetics

- Mean terminal half-life 27–32 hours
- Steady-state plasma concentrations achieved within 1 week
- No significant actions on CYP450 enzymes



Drug Interactions

- Tramadol increases the risk of seizures in patients taking an antidepressant
- Can cause a fatal “serotonin syndrome” when combined with MAOIs, so do not use with MAOIs or for at least 14 days after MAOIs are stopped
- Do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing escitalopram
- Could theoretically cause weakness, hyperreflexia, and incoordination when combined with sumatriptan or possibly other triptans, requiring careful monitoring of patient
- Possible increased risk of bleeding, especially when combined with anticoagulants (e.g., warfarin, NSAIDs)
- NSAIDs may impair effectiveness of SSRIs
- Few known adverse drug interactions



Other Warnings/ Precautions

- Use with caution in patients with history of seizures
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies

- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is taking an MAOI
- If patient is taking pimozide
- If there is a proven allergy to escitalopram or citalopram

SPECIAL POPULATIONS

Renal Impairment

- No dose adjustment for mild to moderate impairment
- Use cautiously in patients with severe impairment

Hepatic Impairment

- Recommended dose 10 mg/day

Cardiac Impairment

- Not systematically evaluated in patients with cardiac impairment
- Preliminary data suggest that citalopram is safe in patients with cardiac impairment, suggesting that escitalopram is also safe
- Treating depression with SSRIs in patients with acute angina or following myocardial infarction may reduce cardiac events and improve survival as well as mood

Elderly

- Recommended dose 10 mg/day
- Risk of SIADH with SSRIs is higher in the elderly
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Approved for depression in adolescents ages 12–17
- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart

- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester
- Nonetheless, continuous treatment during pregnancy may be necessary and has not been proven to be harmful to the fetus
- At delivery there may be more bleeding in the mother and transient irritability or sedation in the newborn
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients, this may mean continuing treatment during pregnancy
- Exposure to SSRIs early in pregnancy may be associated with increased risk of septal heart defects (absolute risk is small)
- SSRI use beyond the 20th week of pregnancy may be associated with increased risk of pulmonary hypertension in newborns, although this is not proven
- Exposure to SSRIs late in pregnancy may be associated with increased risk of gestational hypertension and preeclampsia
- Neonates exposed to SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support,

and tube feeding; reported symptoms are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome, and include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying.

Breast Feeding

- Some drug is found in mother's breast milk
- Trace amounts may be present in nursing children whose mothers are on escitalopram
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients, this may mean continuing treatment during breast feeding

- Panic attacks, avoidant behavior, re-experiencing, hyperarousal
- Sleep disturbance, both insomnia and hypersomnia



Pearls

- May be among the best-tolerated antidepressants
- May have less sexual dysfunction than some other SSRIs
- May be better tolerated than citalopram
- Can cause cognitive and affective "flattening"
- R-citalopram may interfere with the binding of S-citalopram at the serotonin transporter
- For this reason, S-citalopram may be more than twice as potent as R,S-citalopram (i.e., citalopram)
- Thus, 10 mg starting dose of S-citalopram may have the therapeutic efficacy of 40 mg of R,S-citalopram
- Thus, escitalopram may have faster onset and better efficacy with reduced side effects compared to R,S-citalopram
- Some data may actually suggest remission rates comparable to SNRIs, but this is not proven
- Escitalopram is commonly used with augmenting agents, as it is the SSRI with the least interaction at either CYP450 2D6 or 3A4, therefore causing fewer pharmacokinetically mediated drug interactions with augmenting agents than other SSRIs
- SSRIs may be less effective in women over 50, especially if they are not taking estrogen
- SSRIs may be useful for hot flushes in perimenopausal women
- Some postmenopausal women's depression will respond better to escitalopram plus estrogen augmentation than to escitalopram alone
- Nonresponse to escitalopram in elderly may require consideration of mild cognitive impairment or Alzheimer disease

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients taking concomitant medications (few drug interactions and fewer even than with citalopram)
- Patients requiring faster onset of action

Potential Disadvantages

- More expensive than citalopram in markets where citalopram is generic

Primary Target Symptoms

- Depressed mood
- Anxiety



Suggested Reading

Baldwin DS, Reines EH, Guiton C, Weiller E. Escitalopram therapy for major depression and anxiety disorders. *Ann Pharmacother* 2007;41(10):1583–92.

Bareggi SR, Mundo E, Dell-Osso B, Altamura AC. The use of escitalopram beyond major depression: pharmacological

aspects, efficacy and tolerability in anxiety disorders. *Expert Opin Drug Metab Toxicol* 2007;3(5):741–53.

Burke WJ. Escitalopram. *Expert Opin Investig Drugs* 2002;11(10):1477–86.

THERAPEUTICS

Brands

- Prozac
- Prozac weekly
- Sarafem

see index for additional brand names

Generic? Yes**Class**

- Neuroscience-based Nomenclature: serotonin reuptake inhibitor (S-RI)
- SSRI (selective serotonin reuptake inhibitor); often classified as an antidepressant, but it is not just an antidepressant

Commonly Prescribed for

(bold for FDA approved)

- Major depressive disorder (ages 8 and older)
- Obsessive-compulsive disorder (OCD) (ages 7 and older)
- Premenstrual dysphoric disorder (PMDD)
- Bulimia nervosa
- Panic disorder
- Bipolar depression [in combination with olanzapine (Symbax)]
- Treatment-resistant depression [in combination with olanzapine (Symbax)]
- Social anxiety disorder (social phobia)
- Posttraumatic stress disorder (PTSD)

**How the Drug Works**

- Boosts neurotransmitter serotonin
- Blocks serotonin reuptake pump (serotonin transporter)
- Desensitizes serotonin receptors, especially serotonin 1A receptors
- Presumably increases serotonergic neurotransmission
- Fluoxetine also has antagonist properties at 5HT2C receptors, which could increase norepinephrine and dopamine neurotransmission

How Long Until It Works

- ✳ Some patients may experience increased energy or activation early after initiation of treatment
- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks

- If it is not working within 6–8 weeks, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Continue treatment until all symptoms are gone (remission) or significantly reduced (e.g., OCD, PTSD)
- Once symptoms are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- For anxiety disorders and bulimia, treatment may also need to be indefinite

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating in depression)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some patients who have an initial response may relapse even though they continue treatment, sometimes called "poop-out"
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer

**Best Augmenting Combos for Partial Response or Treatment Resistance**

- Trazodone, especially for insomnia

- Bupropion, mirtazapine, reboxetine, or atomoxetine (add with caution and at lower doses since fluoxetine could theoretically raise atomoxetine levels); use combinations of antidepressants with caution as this may activate bipolar disorder and suicidal ideation
- Modafinil, especially for fatigue, sleepiness, and lack of concentration
- Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression, treatment-resistant depression, or treatment-resistant anxiety disorders
- ✿ Fluoxetine has been specifically studied in combination with olanzapine (olanzapine-fluoxetine combination) with excellent results for bipolar depression, treatment-resistant unipolar depression, and psychotic depression
- Benzodiazepines
- If all else fails for anxiety disorders, consider gabapentin or tiagabine
- Hypnotics for insomnia
- Classically, lithium, buspirone, or thyroid hormone

Tests

- None for healthy individuals

SIDE EFFECTS

How Drug Causes Side Effects

- Theoretically due to increases in serotonin concentrations at serotonin receptors in parts of the brain and body other than those that cause therapeutic actions (e.g., unwanted actions of serotonin in sleep centers causing insomnia, unwanted actions of serotonin in the gut causing diarrhea, etc.)
- Increasing serotonin can cause diminished dopamine release and might contribute to emotional flattening, cognitive slowing, and apathy in some patients
- Most side effects are immediate but often go away with time, in contrast to most therapeutic effects which are delayed and are enhanced over time
- ✿ Fluoxetine's unique 5HT2C antagonist properties could contribute to agitation, anxiety, and undesirable activation, especially early in dosing

Notable Side Effects

- Sexual dysfunction (men: delayed ejaculation, erectile dysfunction; men and women: decreased sexual desire, anorgasmia)
- Gastrointestinal (decreased appetite, nausea, diarrhea, constipation, dry mouth)
- Mostly CNS (insomnia but also sedation, agitation, tremors, headache, dizziness)
- Note: patients with diagnosed or undiagnosed bipolar or psychotic disorders may be more vulnerable to CNS-activating actions of SSRIs
- Autonomic (sweating)
- Bruising and rare bleeding
- SIADH (syndrome of inappropriate antidiuretic hormone secretion)



Life-Threatening or Dangerous Side Effects

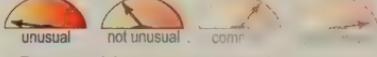
- Rare seizures
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Reported but not expected
- Possible weight loss, especially short-term

Sedation



- Reported but not expected

What to Do About Side Effects

- Wait
- Wait
- Wait
- If fluoxetine is activating, take in the morning to help reduce insomnia
- Reduce dose to 10 mg, and either stay at this dose if tolerated and effective, or consider increasing again to 20 mg or more if tolerated but not effective at 10 mg
- In a few weeks, switch or add other drugs

Best Augmenting Agents for Side Effects

- Often best to try another SSRI or another antidepressant monotherapy prior to

- resorting to augmentation strategies to treat side effects
- Trazodone or a hypnotic for insomnia
- Bupropion, sildenafil, vardenafil, or tadalafil for sexual dysfunction
- Bupropion for emotional flattening, cognitive slowing, or apathy
- Mirtazapine for insomnia, agitation, and gastrointestinal side effects
- Benzodiazepines for jitteriness and anxiety, especially at initiation of treatment and especially for anxious patients
- Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of fluoxetine

DOSING AND USE

Usual Dosage Range

- 20–80 mg for depression and anxiety disorders
- 60–80 mg for bulimia

Dosage Forms

- Capsules 10 mg, 20 mg, 40 mg, 60 mg
- Tablet 10 mg
- Liquid 20 mg/5 mL–120 mL bottles
- Weekly capsule 90 mg

How to Dose

- Depression and OCD: initial dose 20 mg/day in morning, usually wait a few weeks to assess drug effects before increasing dose; maximum dose generally 80 mg/day
- Bulimia: initial dose 60 mg/day in morning; some patients may need to begin at lower dose and titrate over several days



Dosing Tips

- The long half-lives of fluoxetine and its active metabolites mean that dose changes

will not be fully reflected in plasma for several weeks, lengthening titration to final dose and extending withdrawal from treatment

- Give once daily, often in the mornings, but at any time of day tolerated
- Often available in capsules, not tablets, so unable to break capsules in half
- Occasional patients are dosed above 80 mg
- Liquid formulation easiest for doses below 10 mg when used for cases that are very intolerant to fluoxetine or for very slow up and down titration needs
- For some patients, weekly dosing with the weekly formulation may enhance compliance
- The more anxious and agitated the patient, the lower the starting dose, the slower the titration, and the more likely the need for a concomitant agent such as trazodone or a benzodiazepine
- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar disorder and switch to a mood stabilizer or an atypical antipsychotic

Overdose

- Rarely lethal in monotherapy overdose; respiratory depression especially with alcohol, ataxia, sedation, possible seizures

Long-Term Use

- Safe

Habit Forming

- No

How to Stop

- Taper rarely necessary since fluoxetine tapers itself after immediate discontinuation, due to the long half-life of fluoxetine and its active metabolites

Pharmacokinetics

- Active metabolite (norfluoxetine) has 2 week half-life
- Parent drug has 2–3 day half-life
- Inhibits CYP450 2D6
- Inhibits CYP450 3A4



Drug Interactions

- Tramadol increases the risk of seizures in patients taking an antidepressant

- Can increase TCA levels; use with caution with TCAs or when switching from a TCA to fluoxetine
- Can cause a fatal "serotonin syndrome" when combined with MAOIs, so do not use with MAOIs or for at least 14 days after MAOIs are stopped
- Do not start an MAOI for at least 5 weeks after discontinuing fluoxetine
- May displace highly protein bound drugs (e.g., warfarin)
- Can rarely cause weakness, hyperreflexia, and incoordination when combined with sumatriptan, or possibly with other triptans, requiring careful monitoring of patient
- Possible increased risk of bleeding, especially when combined with anticoagulants (e.g., warfarin, NSAIDs)
- NSAIDs may impair effectiveness of SSRIs
- Via CYP450 2D6 inhibition, could theoretically interfere with the analgesic actions of codeine, and increase the plasma levels of some beta blockers and of atomoxetine
- Via CYP450 2D6 inhibition, fluoxetine could theoretically increase concentrations of thioridazine and cause dangerous cardiac arrhythmias
- May reduce the clearance of diazepam or trazodone, thus increasing their levels
- Via CYP450 3A4 inhibition, may increase the levels of alprazolam, buspirone, and triazolam
- Via CYP450 3A4 inhibition, fluoxetine could theoretically increase concentrations of certain cholesterol lowering HMG CoA reductase inhibitors, especially simvastatin, atorvastatin, and lovastatin, but not pravastatin or fluvastatin, which would increase the risk of rhabdomyolysis; thus, coadministration of fluoxetine with certain HMG CoA reductase inhibitors should proceed with caution
- Via CYP450 3A4 inhibition, fluoxetine could theoretically increase the concentrations of pimozide, and cause QTc prolongation and dangerous cardiac arrhythmias



Other Warnings/ Precautions

- Add or initiate other antidepressants with caution for up to 5 weeks after discontinuing fluoxetine
- Use with caution in patients with history of seizure
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is taking an MAOI
- If patient is taking thioridazine
- If patient is taking pimozide
- If patient is taking tamoxifen
- If there is a proven allergy to fluoxetine

SPECIAL POPULATIONS

Renal Impairment

- No dose adjustment
- Not removed by hemodialysis

Hepatic Impairment

- Lower dose or give less frequently, perhaps by half

Cardiac Impairment

- Preliminary research suggests that fluoxetine is safe in these patients
- Treating depression with SSRIs in patients with acute angina or following myocardial infarction may reduce cardiac events and improve survival as well as mood

Elderly

- Some patients may tolerate lower doses better
- Risk of SIADH with SSRIs is higher in the elderly
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Approved for OCD and depression
- Adolescents often receive adult dose, but doses slightly lower for children
- Children taking fluoxetine may have slower growth; long-term effects are unknown



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester
- Nonetheless, continuous treatment during pregnancy may be necessary and has not been proven to be harmful to the fetus
- Current patient registries of children whose mothers took fluoxetine during pregnancy do not show adverse consequences

- At delivery there may be more bleeding in the mother and transient irritability or sedation in the newborn
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy
- Exposure to SSRIs early in pregnancy may be associated with increased risk of septal heart defects (absolute risk is small)
- SSRI use beyond the 20th week of pregnancy may be associated with increased risk of pulmonary hypertension in newborns, although this is not proven
- Exposure to SSRIs late in pregnancy may be associated with increased risk of gestational hypertension and preeclampsia
- Neonates exposed to SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding; reported symptoms are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome, and include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying

Breast Feeding

- Some drug is found in mother's breast milk
- Trace amounts may be present in nursing children whose mothers are on fluoxetine
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY**Potential Advantages**

- Patients with atypical depression (hypersomnia, increased appetite)
- Patients with fatigue and low energy
- Patients with comorbid eating and affective disorders
- Generic is less expensive than brand name where available
- Patients for whom weekly administration is desired
- Children with OCD or depression

Potential Disadvantages

- Patients with anorexia
- Initiating treatment in anxious, agitated patients
- Initiating treatment in severe insomnia

Primary Target Symptoms

- Depressed mood
- Energy, motivation, and interest
- Anxiety (eventually, but can actually increase anxiety, especially short-term)
- Sleep disturbance, both insomnia and hypersomnia (eventually, but may actually cause insomnia, especially short-term)

**Pearls**

- May be a first-line choice for atypical depression (e.g., hypersomnia, hyperphagia, low energy, mood reactivity)
- Consider avoiding in agitated insomniacs
- Can cause cognitive and affective “flattening”
- Not as well tolerated as some other SSRIs for panic disorder and other anxiety disorders, especially when dosing is

**Suggested Reading**

Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *J Affect Disord* 2000;58:19–36.

Beasley CM Jr, Ball SG, Nilsson ME, et al. Fluoxetine and adult suicidality revisited: an updated meta-analysis using expanded data sources from placebo-controlled trials. *J Clin Psychopharmacol* 2007;27(6):682–6.

- initiated, unless given with co-therapies such as benzodiazepines or trazodone
- Long half-life; even longer lasting active metabolite
- Actions at 5HT2C receptors may explain its activating properties
- Actions at 5HT2C receptors may explain in part fluoxetine's efficacy in combination with olanzapine for bipolar depression and treatment-resistant depression, since both agents have this property
- For sexual dysfunction, can augment with bupropion, sildenafil, vardenafil, or tadalafil, or switch to a non-SSRI such as bupropion or mirtazapine
- Mood disorders can be associated with eating disorders (especially in adolescent females) and be treated successfully with fluoxetine
- SSRIs may be less effective in women over 50, especially if they are not taking estrogen
- SSRIs may be useful for hot flushes in perimenopausal women
- Some postmenopausal women's depression will respond better to fluoxetine plus estrogen augmentation than to fluoxetine alone
- Nonresponse to fluoxetine in elderly may require consideration of mild cognitive impairment or Alzheimer disease
- SSRIs may not cause as many patients to attain remission of depression as some other classes of antidepressants (e.g., SNRIs)
- A single pill containing both fluoxetine and olanzapine is available for combination treatment of bipolar depression, psychotic depression, and treatment-resistant unipolar depression

March JS, Silva S, Petrycki S, et al. The treatment for adolescents with depression study (TADS): long-term effectiveness and safety outcomes. *Arch Gen Psychiatry* 2007;64(10):1132–43.

Wagstaff AJ, Goa KL. Once-weekly fluoxetine. *Drugs* 2001;61:2221–8.

THERAPEUTICS

Brands • Depixol

see index for additional brand names

Generic? No**Class**

- Neuroscience-based Nomenclature: dopamine receptor antagonist (D-RAn)
- Conventional antipsychotic (neuroleptic, thioxanthene, dopamine 2 antagonist)

Commonly Prescribed for

(bold for FDA approved)

- Schizophrenia
- Depression (low dose)
- Other psychotic disorders
- Bipolar disorder

**How the Drug Works**

- Blocks dopamine 2 receptors, reducing positive symptoms of psychosis

How Long Until It Works

- With injection, psychotic symptoms can improve within a few days, but it may take 1–2 weeks for notable improvement
- With oral formulation, psychotic symptoms can improve within 1 week, but it may take several weeks for full effect on behavior

If It Works

- Most often reduces positive symptoms in schizophrenia but does not eliminate them
- Most schizophrenic patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third
- Continue treatment in schizophrenia until reaching a plateau of improvement
- After reaching a satisfactory plateau, continue treatment for at least a year after first episode of psychosis in schizophrenia
- For second and subsequent episodes of psychosis in schizophrenia, treatment may need to be indefinite
- Reduces symptoms of acute psychotic mania but not proven as a mood stabilizer or as an effective maintenance treatment in bipolar disorder
- After reducing acute psychotic symptoms in mania, switch to a mood stabilizer and/or an atypical antipsychotic for mood stabilization and maintenance

If It Doesn't Work

- Consider trying one of the first-line atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, amisulpride)
- Consider trying another conventional antipsychotic
- If 2 or more antipsychotic monotherapies do not work, consider clozapine

**Best Augmenting Combos for Partial Response or Treatment Resistance**

- Augmentation of conventional antipsychotics has not been systematically studied
- Addition of a mood-stabilizing anticonvulsant such as valproate, carbamazepine, or lamotrigine may be helpful in both schizophrenia and bipolar mania
- Augmentation with lithium in bipolar mania may be helpful
- Addition of a benzodiazepine, especially short-term for agitation

Tests

✳ Since conventional antipsychotics are frequently associated with weight gain, before starting treatment, weigh all patients and determine if the patient is already overweight (BMI 25.0–29.9) or obese (BMI ≥30)

• Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–125 mg/dL), diabetes (fasting plasma glucose >126 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management

✳ Monitor weight and BMI during treatment

✳ Consider monitoring fasting triglycerides monthly for several months in patients at high risk for metabolic complications and when initiating or switching antipsychotics

✳ While giving a drug to a patient who has gained >5% of initial weight, consider evaluating for the presence of pre-diabetes,

diabetes, or dyslipidemia, or consider switching to a different antipsychotic

- Monitoring elevated prolactin levels of dubious clinical benefit
- Patients with low white blood cell count (WBC) or history of drug-induced leucopenia/neutropenia should have complete blood count (CBC) monitored frequently during the first few months and flupentixol should be discontinued at the first sign of decline of WBC in the absence of other causative factors

SIDE EFFECTS

How Drug Causes Side Effects

- By blocking dopamine 2 receptors in the striatum, it can cause motor side effects
- By blocking dopamine 2 receptors in the pituitary, it can cause elevations in prolactin
- By blocking dopamine 2 receptors excessively in the mesocortical and mesolimbic dopamine pathways, especially at high doses, it can cause worsening of negative and cognitive symptoms (neuroleptic-induced deficit syndrome)
- Anticholinergic actions may cause sedation, blurred vision, constipation, dry mouth
- Antihistaminic actions may cause sedation, weight gain
- By blocking alpha 1 adrenergic receptors, it can cause dizziness, sedation, and hypotension
- Mechanism of weight gain and any possible increased incidence of diabetes or dyslipidemia with conventional antipsychotics is unknown

Notable Side Effects

- ✿ Neuroleptic-induced deficit syndrome
- ✿ Extrapyramidal symptoms (more common at start of treatment), parkinsonism
- ✿ Insomnia, restlessness, agitation, sedation
- ✿ Tardive dyskinesia (risk increases with duration of treatment and with dose)
- ✿ Galactorrhea, amenorrhea
- Tachycardia
- Weight gain
- Hypomania
- Rare eosinophilia



Life-Threatening or Dangerous Side Effects

- Rare neuroleptic malignant syndrome
- Rare seizures
- Rare jaundice, leucopenia
- Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis

Weight Gain



- Many experience and/or can be significant in amount

Sedation



- Occurs in significant minority

What to Do About Side Effects

- Wait
- Wait
- Wait
- For motor symptoms, add an anticholinergic agent
- Reduce the dose
- For sedation, give at night
- Switch to an atypical antipsychotic
- Weight loss, exercise programs, and medical management for high BMIs, diabetes, dyslipidemia

Best Augmenting Agents for Side Effects

- Benztrapine or trihexyphenidyl for motor side effects
- Sometimes amantadine can be helpful for motor side effects
- Benzodiazepines may be helpful for akathisia
- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- Oral 3–6 mg/day in divided doses
- Intramuscular 40–120 mg every 1–4 weeks

Dosage Forms

- Tablet 0.5 mg, 3 mg
- Injection 20 mg/mL, 100 mg/mL

How to Dose

- Oral: initial 1 mg 3 times a day; increase by 1 mg every 2–3 days; maximum generally 18 mg/day
- Intramuscular: initial dose 20 mg for patients who have not been exposed to long-acting depot antipsychotics, 40 mg for patients who have previously demonstrated tolerance to long-acting depot antipsychotics; after 4–10 days can give additional 20 mg dose; maximum 200 mg every 1–4 weeks



Dosing Tips

- The peak of action for the decanoate is usually 7–10 days, and doses generally have to be administered every 2–3 weeks
- May have more activating effects at low doses, which can sometimes be useful as a second-line, short-term treatment of depression
- Some evidence that flupenthixol may improve anxiety and depression at low doses
- Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³

Overdose

- Agitation, confusion, sedation, extrapyramidal symptoms, respiratory collapse, circulatory collapse

Long-Term Use

- Safe

Habit Forming

- No

How to Stop

- Slow down-titration of oral formulation (over 6–8 weeks), especially when simultaneously beginning a new antipsychotic while switching (i.e., cross-titration)
- Rapid oral discontinuation may lead to rebound psychosis and worsening of symptoms
- If antiparkinson agents are being used, they should be continued for a few weeks after flupenthixol is discontinued

Pharmacokinetics

- Oral: maximum plasma concentrations within 3–8 hours

- Intramuscular: rate-limiting half-life approximately 8 days with single dose, approximately 17 days with multiple doses



Drug Interactions

- May decrease the effects of levodopa, dopamine agonists
- May increase the effects of antihypertensive drugs except for guanethidine, whose antihypertensive actions flupenthixol may antagonize
- CNS effects may be increased if used with other CNS depressants
- Combined use with epinephrine may lower blood pressure
- Ritonavir may increase plasma levels of flupenthixol
- May increase carbamazepine plasma levels
- Some patients taking a neuroleptic and lithium have developed an encephalopathic syndrome similar to neuroleptic malignant syndrome



Other Warnings/ Precautions

- If signs of neuroleptic malignant syndrome develop, treatment should be immediately discontinued
- Use cautiously in patients with alcohol withdrawal or convulsive disorders because of possible lowering of seizure threshold
- In epileptic patients, dose 10–20 mg every 15 days for intramuscular formulation
- Use with caution if at all in patients with Parkinson's disease, severe arteriosclerosis, or Lewy body dementia
- Possible antiemetic effect of flupenthixol may mask signs of other disorders or overdose; suppression of cough reflex may cause asphyxia
- Avoid extreme heat exposure
- Do not use epinephrine in event of overdose as interaction with some pressor agents may lower blood pressure

Do Not Use

- If patient is taking a large concomitant dose of a sedative hypnotic
- If patient has CNS depression
- If patient is comatose or if there is brain damage
- If there is blood dyscrasia
- If patient has pheochromocytoma

- If patient has liver damage
- If patient has a severe cardiovascular disorder
- If patient has renal insufficiency
- If patient has cerebrovascular insufficiency
- If there is a proven allergy to flupenthixol

SPECIAL POPULATIONS

Renal Impairment

- Oral: recommended to take half or less of usual adult dose
- Intramuscular: recommended dose schedule generally 10–20 mg every 15 days

Hepatic Impairment

- Use with caution
- Oral: recommended to take half or less of usual adult dose

Cardiac Impairment

- Use with caution
- Oral: recommended to take half or less of usual adult dose

Elderly

- Intramuscular: recommended initial dose generally 5 mg; recommended dose schedule generally 10–20 mg every 15 days
- Oral: recommended to take half or less of usual adult dose
- Although conventional antipsychotics are commonly used for behavioral disturbances in dementia, no agent has been approved for treatment of elderly patients with dementia-related psychosis
- Elderly patients with dementia-related psychosis treated with antipsychotics are at increased risk of death compared to placebo, and also have an increased risk of cerebrovascular events



Children and Adolescents

- Not recommended for use in children



Pregnancy

- Not recommended for use during pregnancy

- There is a risk of abnormal muscle movements and withdrawal symptoms in newborns whose mothers took an antipsychotic during the third trimester; symptoms may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty feeding
- Reports of extrapyramidal symptoms, jaundice, hyperreflexia, hyporeflexia in infants whose mothers took a conventional antipsychotic during pregnancy
- Psychotic symptoms may worsen during pregnancy and some form of treatment may be necessary
- Atypical antipsychotics may be preferable to conventional antipsychotics or anticonvulsant mood stabilizers if treatment is required during pregnancy

Breast Feeding

- Some drug is found in mother's breast milk
- ✖ Recommended either to discontinue drug or bottle feed

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Noncompliant patients

Potential Disadvantages

- Children
- Elderly
- Patients with tardive dyskinesia

Primary Target Symptoms

- Positive symptoms of psychosis
- Negative symptoms of psychosis
- Aggressive symptoms



Pearls

- Less sedation and orthostatic hypotension but more extrapyramidal symptoms than some other conventional antipsychotics
- Patients have very similar antipsychotic responses to any conventional antipsychotic, which is different from atypical antipsychotics where antipsychotic responses of individual patients can occasionally vary greatly from one atypical antipsychotic to another

- Patients with inadequate responses to atypical antipsychotics may benefit from a trial of augmentation with a conventional antipsychotic such as flupenthixol or from switching to a conventional antipsychotic such as flupenthixol
- However, long-term polypharmacy with a combination of a conventional antipsychotic such as flupenthixol with an atypical antipsychotic may combine their side effects without clearly augmenting the efficacy of either
- For treatment-resistant patients, especially those with impulsivity, aggression, violence, and self-harm, long-term polypharmacy with 2 atypical antipsychotics or with 1 atypical antipsychotic and 1 conventional antipsychotic may be useful or even necessary while closely monitoring
- In such cases, it may be beneficial to combine 1 depot antipsychotic with 1 oral antipsychotic
- Although a frequent practice by some prescribers, adding 2 conventional antipsychotics together has little rationale and may reduce tolerability without clearly enhancing efficacy



Suggested Reading

Gerlach J. Depot neuroleptics in relapse prevention: advantages and disadvantages. *Int Clin Psychopharmacol* 1995;(9 Suppl 5):S17–20.

Quraishi S, David A. Depot flupenthixol decanoate for schizophrenia or other similar psychotic disorders. *Cochrane Database Syst Rev* 2000;(2):CD001470.

Soyka M, De Vry J. Flupenthixol as a potential pharmacotreatment of alcohol and cocaine abuse/dependence. *Eur Neuropsychopharmacol* 2000;10(5):325–32.

THERAPEUTICS

Brands

- Luvox

- Luvox CR

see index for additional brand names

Generic?

Yes (not for fluvoxamine CR)



Class

- Neuroscience-based Nomenclature: serotonin reuptake inhibitor (S-RI)
- SSRI (selective serotonin reuptake inhibitor); often classified as an antidepressant, but it is not just an antidepressant

Commonly Prescribed for

(bold for FDA approved)

- **Obsessive-compulsive disorder (OCD) (fluvoxamine and fluvoxamine CR)**
- **Social anxiety disorder (fluvoxamine CR)**
- Depression
- Panic disorder
- Generalized anxiety disorder (GAD)
- Posttraumatic stress disorder (PTSD)



How the Drug Works

- Boosts neurotransmitter serotonin
 - Blocks serotonin reuptake pump (serotonin transporter)
 - Desensitizes serotonin receptors, especially serotonin 1A receptors
 - Presumably increases serotonergic neurotransmission
- ✿ Fluvoxamine also binds at sigma 1 receptors

How Long Until It Works

- ✿ Some patients may experience relief of insomnia or anxiety early after initiation of treatment
- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
 - If it is not working within 6–8 weeks, it may require a dosage increase or it may not work at all
 - May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure

since symptoms can recur after medicine stopped

- Continue treatment until all symptoms are gone (remission) or significantly reduced (e.g., OCD)
- Once symptoms gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders may also need to be indefinite

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating in depression)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some patients who have an initial response may relapse even though they continue treatment, sometimes called “poop-out”
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer



Best Augmenting Combos for Partial Response or Treatment Resistance

- For the expert, consider cautious addition of clomipramine for treatment-resistant OCD
- Trazodone, especially for insomnia
- Bupropion, mirtazapine, reboxetine, or atomoxetine (use combinations of antidepressants with caution as this may activate bipolar disorder and suicidal ideation)
- Modafinil, especially for fatigue, sleepiness, and lack of concentration
- Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression, treatment-resistant depression, or treatment-resistant anxiety disorders

- Benzodiazepines
- If all else fails for anxiety disorders, consider gabapentin or tiagabine
- Hypnotics for insomnia
- Classically, lithium, buspirone, or thyroid hormone
- In Europe and Japan, augmentation is more commonly administered for the treatment of depression and anxiety disorders, especially with benzodiazepines and lithium
- In the USA, augmentation is more commonly administered for the treatment of OCD, especially with atypical antipsychotics, buspirone, or even clomipramine; clomipramine should be added with caution and at low doses as fluvoxamine can alter clomipramine metabolism and raise its levels

Tests

- None for healthy individuals

SIDE EFFECTS

How Drug Causes Side Effects

- Theoretically due to increases in serotonin concentrations at serotonin receptors in parts of the brain and body other than those that cause therapeutic actions (e.g., unwanted actions of serotonin in sleep centers causing insomnia, unwanted actions of serotonin in the gut causing diarrhea, etc.)
- Increasing serotonin can cause diminished dopamine release and might contribute to emotional flattening, cognitive slowing, and apathy in some patients
- Most side effects are immediate but often go away with time, in contrast to most therapeutic effects which are delayed and are enhanced over time
- **Fluvoxamine's sigma 1 antagonist properties may contribute to sedation and fatigue in some patients**

Notable Side Effects

- Sexual dysfunction (men: delayed ejaculation, erectile dysfunction; men and women: decreased sexual desire, anorgasmia)
- Gastrointestinal (decreased appetite, nausea, diarrhea, constipation, dry mouth)

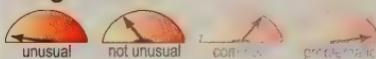
- Mostly CNS (insomnia but also sedation, agitation, tremors, headache, dizziness)
- Note: patients with diagnosed or undiagnosed bipolar or psychotic disorders may be more vulnerable to CNS-activating actions of SSRIs
- Autonomic (sweating)
- Bruising and rare bleeding
- Rare hyponatremia



Life-Threatening or Dangerous Side Effects

- Rare seizures
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Reported but not expected
- Patients may actually experience weight loss

Sedation



- Many experience and/or can be significant in amount

What to Do About Side Effects

- Wait
- Wait
- Wait
- If fluvoxamine is sedating, take at night to reduce drowsiness
- Reduce dose
- In a few weeks, switch or add other drugs

Best Augmenting Agents for Side Effects

- Often best to try another SSRI or another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
- Trazodone or a hypnotic for insomnia
- Bupropion, sildenafil, vardenafil, or tadalafil for sexual dysfunction
- Bupropion for emotional flattening, cognitive slowing, or apathy

- Mirtazapine for insomnia, agitation, and gastrointestinal side effects
- Benzodiazepines for jitteriness and anxiety, especially at initiation of treatment and especially for anxious patients
- Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of fluvoxamine



Dosing Tips

- 50-mg and 100-mg tablets are scored, so to save costs, give 25 mg as half of 50 mg tablet, and give 50 mg as half of 100 mg tablet
- To improve tolerability of immediate-release formulation, dosing can either be given once a day, usually all at night, or split either symmetrically or asymmetrically, usually with more of the dose given at night
- Some patients take more than 300 mg/day
- Controlled-release capsules should not be chewed or crushed
- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar disorder and switch to a mood stabilizer or an atypical antipsychotic

DOSING AND USE

Usual Dosage Range

- 100–300 mg/day for OCD
- 100–200 mg/day for depression
- 100–300 mg/day for social anxiety disorder

Dosage Forms

- Tablets 25 mg, 50 mg scored, 100 mg scored
- Controlled-release capsules 100 mg, 150 mg

How to Dose

- For immediate-release, initial 50 mg/day; increase by 50 mg/day in 4–7 days; usually wait a few weeks to assess drug effects before increasing dose further, but can increase by 50 mg/day every 4–7 days until desired efficacy is reached; maximum 300 mg/day
- For immediate-release, doses below 100 mg/day usually given as a single dose at bedtime; doses above 100 mg/day can be divided into two doses to enhance tolerability, with the larger dose administered at night, but can also be given as a single dose at bedtime
- For controlled-release, initial 100 mg/day; increase by 50 mg/day each week until desired efficacy is reached; maximum generally 300 mg/day

Overdose

- Rare fatalities have been reported, both in combination with other drugs and alone; sedation, dizziness, vomiting, diarrhea, irregular heartbeat, seizures, coma, breathing difficulty

Long-Term Use

- Safe

Habit Forming

- No

How to Stop

- Taper to avoid withdrawal effects (dizziness, nausea, stomach cramps, sweating, tingling, dysesthesias)
- Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation
- If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly

Pharmacokinetics

- Parent drug has 9–28 hour half-life
- Inhibits CYP450 3A4
- Inhibits CYP450 1A2
- Inhibits CYP450 2C9/2C19



Drug Interactions

- Tramadol increases the risk of seizures in patients taking an antidepressant
- Can increase tricyclic antidepressant levels; use with caution with TCAs
- Can cause a fatal "serotonin syndrome" when combined with MAOIs, so do not use with MAOIs or for at least 14 days after MAOIs are stopped
- Do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing fluvoxamine
- May displace highly protein-bound drugs (e.g., warfarin)
- Can rarely cause weakness, hyperreflexia, and incoordination when combined with sumatriptan or possibly with other triptans, requiring careful monitoring of patient
- Possible increased risk of bleeding, especially when combined with anticoagulants (e.g., warfarin, NSAIDs)
- NSAIDs may impair effectiveness of SSRIs
- Via CYP450 1A2 inhibition, fluvoxamine may reduce clearance of theophylline and clozapine, thus raising their levels and requiring their dosing to be lowered
- Fluvoxamine administered with either caffeine or theophylline can thus cause jitteriness, excessive stimulation, or rarely seizures, so concomitant use should proceed cautiously
- Metabolism of fluvoxamine may be enhanced in smokers and thus its levels lowered, requiring higher dosing
- Via CYP450 3A4 inhibition, fluvoxamine may reduce clearance of carbamazepine and benzodiazepines such as alprazolam and triazolam, and thus require dosage reduction
- Via CYP450 3A4 inhibition, fluvoxamine could theoretically increase concentrations of certain cholesterol lowering HMG CoA reductase inhibitors, especially simvastatin, atorvastatin, and lovastatin, but not pravastatin or fluvastatin, which would increase the risk of rhabdomyolysis; thus, coadministration of fluvoxamine with certain HMG CoA reductase inhibitors should proceed with caution

- Via CYP450 3A4 inhibition, fluvoxamine could theoretically increase the concentrations of pimozide, and cause QTc prolongation and dangerous cardiac arrhythmias



Other Warnings/ Precautions

- Add or initiate other antidepressants with caution for up to 2 weeks after discontinuing fluvoxamine
- Use with caution in patients with history of seizure
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- May cause photosensitivity
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is taking an MAOI
- If patient is taking thioridazine, pimozide, tizanidine, alosetron, or ramelteon
- If there is a proven allergy to fluvoxamine

SPECIAL POPULATIONS

Renal Impairment

- Consider lower initial dose

Hepatic Impairment

- Lower dose or give less frequently, perhaps by half; use slower titration

Cardiac Impairment

- Preliminary research suggests that fluvoxamine is safe in these patients
- Treating depression with SSRIs in patients with acute angina or following myocardial infarction may reduce cardiac events and improve survival as well as mood

Elderly

- May require lower initial dose and slower titration
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older

**Children and Adolescents**

- Immediate-release approved for ages 8–17 for OCD
- 8–17: initial 25 mg/day at bedtime; increase by 25 mg/day every 4–7 days; maximum 200 mg/day; doses above 50 mg/day should be divided into 2 doses with the larger dose administered at bedtime
- Preliminary evidence suggests efficacy for other anxiety disorders and depression in children and adolescents
- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients

**Pregnancy**

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester
- Nonetheless, continuous treatment during pregnancy may be necessary and has not been proven to be harmful to the fetus

- At delivery there may be more bleeding in the mother and transient irritability or sedation in the newborn
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy
- Exposure to SSRIs early in pregnancy may be associated with increased risk of septal heart defects (absolute risk is small)
- SSRI use beyond the 20th week of pregnancy may be associated with increased risk of pulmonary hypertension in newborns, although this is not proven
- Exposure to SSRIs late in pregnancy may be associated with increased risk of gestational hypertension and preeclampsia
- Neonates exposed to SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding; reported symptoms are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome, and include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying

Breast Feeding

- Some drug is found in mother's breast milk
- Trace amounts may be present in nursing children whose mothers are on fluvoxamine
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients with mixed anxiety/depression
- Generic is less expensive than brand name where available

Potential Disadvantages

- Patients with irritable bowel or multiple gastrointestinal complaints
- Can require dose titration and twice daily dosing

Primary Target Symptoms

- Depressed mood
- Anxiety



Pearls

- Often a preferred treatment of anxious depression as well as major depressive disorder comorbid with anxiety disorders
- Some withdrawal effects, especially gastrointestinal effects
- May have lower incidence of sexual dysfunction than other SSRIs
- Preliminary research suggests that fluvoxamine is efficacious in obsessive-compulsive symptoms in schizophrenia when combined with antipsychotics
- Not FDA approved for depression, but used widely for depression in many countries
- CR formulation may be better tolerated than immediate-release formulation, particularly with less sedation
- SSRIs may be less effective in women over 50, especially if they are not taking estrogen

- SSRIs may be useful for hot flushes in perimenopausal women
- Actions at sigma 1 receptors may explain in part fluvoxamine's sometimes rapid onset effects in anxiety disorders and insomnia
- Actions at sigma 1 receptors may explain potential advantages of fluvoxamine for psychotic depression and delusional depression
- For treatment-resistant OCD, consider cautious combination of fluvoxamine and clomipramine by an expert
- Normally, clomipramine (CMI), a potent serotonin reuptake blocker, at steady state is metabolized extensively to its active metabolite desmethyl-clomipramine (de-CMI), a potent noradrenergic reuptake blocker
- Thus, at steady state, plasma drug activity is generally more noradrenergic (with higher de-CMI levels) than serotonergic (with lower parent CMI levels)
- Addition of a CYP450 1A2 inhibitor, fluvoxamine, blocks this conversion and results in higher CMI levels than de-CMI levels
- Thus, addition of the SSRI fluvoxamine to CMI in treatment-resistant OCD can powerfully enhance serotonergic activity, not only due to the inherent serotonergic activity of fluvoxamine, but also due to a favorable pharmacokinetic interaction inhibiting CYP450 1A2 and thus converting CMI's metabolism to a more powerful serotonergic portfolio of parent drug



Suggested Reading

Cheer SM, Figgitt DP. Spotlight on fluvoxamine in anxiety disorders in children and adolescents. *CNS Drugs* 2002;16:139–44.

Edwards JG, Anderson I. Systematic review and guide to selection of selective serotonin reuptake inhibitors. *Drugs* 1999;57:507–33.

Figgitt DP, McClellan KJ. Fluvoxamine. An updated review of its use in the management of adults with anxiety disorders. *Drugs* 2000;60:925–54.

Omori M, Watanabe N, Nakagawa A, et al. Fluvoxamine versus other anti-depressive agents for depression. *Cochrane Database Syst Rev* 2010;17(3):CD006114.

Pigott TA, Seay SM. A review of the efficacy of selective serotonin reuptake inhibitors in obsessive-compulsive disorder. *J Clin Psychiatry* 1999;60:101–6.

THERAPEUTICS

Brands • FANAPT*see index for additional brand names***Generic?** No**Class**

- Neuroscience-based Nomenclature: dopamine and serotonin receptor antagonist (DS-RAN)
- Atypical antipsychotic (serotonin-dopamine antagonist; second-generation antipsychotic; also a mood stabilizer)

Commonly Prescribed for*(bold for FDA approved)*

- **Schizophrenia**
- **Schizophrenia maintenance**
- Acute mania/mixed mania
- Other psychotic disorders
- Bipolar maintenance
- Bipolar depression
- Treatment-resistant depression
- Behavioral disturbances in dementia
- Behavioral disturbances in children and adolescents
- Disorders associated with problems with impulse control

**How the Drug Works**

- Blocks dopamine 2 receptors, reducing positive symptoms of psychosis and stabilizing affective symptoms
- Blocks serotonin 2A receptors, causing enhancement of dopamine release in certain brain regions and thus reducing motor side effects and possibly improving cognitive and affective symptoms
- Blockade of central alpha 1 adrenergic receptors may contribute to low potential for EPS

How Long Until It Works

- Psychotic symptoms can improve within 1 week, but it may take several weeks for full effect on behavior as well as on cognition
- Slow titration may delay antipsychotic effects during the first 1 to 2 weeks compared to some other antipsychotic drugs that do not require similar titration

- Classically recommended to wait at least 4–6 weeks to determine efficacy of drug, but in practice some patients may require up to 16–20 weeks to show a good response, especially on cognitive symptoms

If It Works

- Most often reduces positive symptoms but does not eliminate them
- Can improve negative symptoms, as well as aggressive, cognitive, and affective symptoms in schizophrenia
- Most schizophrenia patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third
- Perhaps 5–15% of schizophrenia patients can experience an overall improvement of greater than 50–60%, especially when receiving stable treatment for more than a year
- Such patients are considered super-responders or “awakeners” since they may be well enough to be employed, live independently, and sustain long-term relationships
- Continue treatment until reaching a plateau of improvement
- After reaching a satisfactory plateau, continue treatment for at least a year after first episode of psychosis
- For second and subsequent episodes of psychosis, treatment may need to be indefinite
- Even for first episodes of psychosis, it may be preferable to continue treatment

If It Doesn't Work

- Try one of the other atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, asenapine, lurasidone, amisulpride)
- If 2 or more antipsychotic monotherapies do not work, consider clozapine
- Some patients may require treatment with a conventional antipsychotic
- If no first-line atypical antipsychotic is effective, consider higher doses or augmentation with valproate or lamotrigine
- Consider noncompliance and switch to another antipsychotic with fewer side effects or to an antipsychotic that can be given by depot injection (a depot formulation of iloperidone is in clinical testing)

- Consider initiating rehabilitation and psychotherapy such as cognitive remediation
- Consider presence of concomitant drug abuse



Best Augmenting Combos for Partial Response or Treatment Resistance

- Valproic acid (valproate, divalproex, divalproex ER)
- Other mood-stabilizing anticonvulsants (carbamazepine, oxcarbazepine, lamotrigine)
- Lithium
- Benzodiazepines

Tests

Before starting an atypical antipsychotic

- Weigh all patients and track BMI during treatment
- Get baseline personal and family history of diabetes, obesity, dyslipidemia, hypertension, and cardiovascular disease
- Get waist circumference (at umbilicus), blood pressure, fasting plasma glucose, and fasting lipid profile
- Determine if the patient is
 - overweight (BMI 25.0–29.9)
 - obese (BMI ≥ 30)
 - has pre-diabetes (fasting plasma glucose 100–125 mg/dL)
 - has diabetes (fasting plasma glucose >126 mg/dL)
 - has hypertension (BP $>140/90$ mm Hg)
 - has dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol)
- Treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management

Monitoring after starting an atypical antipsychotic

- BMI monthly for 3 months, then quarterly
- Consider monitoring fasting triglycerides monthly for several months in patients at high risk for metabolic complications and when initiating or switching antipsychotics
- Blood pressure, fasting plasma glucose, fasting lipids within 3 months and then annually, but earlier and more frequently

for patients with diabetes or who have gained $>5\%$ of initial weight

- Treat or refer for treatment and consider switching to another atypical antipsychotic for patients who become overweight, obese, pre-diabetic, diabetic, hypertensive, or dyslipidemic while receiving an atypical antipsychotic

• Even in patients without known diabetes, be vigilant for the rare but life-threatening onset of diabetic ketoacidosis, which always requires immediate treatment, by monitoring for the rapid onset of polyuria, polydipsia, weight loss, nausea, vomiting, dehydration, rapid respiration, weakness, and clouding of sensorium, even coma

- Patients with low white blood cell count (WBC) or history of drug-induced leucopenia/neutropenia should have complete blood count (CBC) monitored frequently during the first few months and iloperidone should be discontinued at the first sign of decline in WBC in the absence of other causative factors
- Patients at risk for electrolyte disturbances (e.g., patients on diuretic therapy) should have baseline and periodic serum potassium and magnesium measurements

SIDE EFFECTS

How Drug Causes Side Effects

- By blocking alpha 1 adrenergic receptors, it can cause dizziness, sedation, and hypotension
- By blocking dopamine 2 receptors in the striatum, it can cause motor side effects
- By blocking dopamine 2 receptors in the pituitary, it can cause elevations in prolactin
- Mechanism of weight gain and increased incidence of diabetes and dyslipidemia with atypical antipsychotics is unknown

Notable Side Effects

- Orthostatic hypotension
- Sedation, dose-dependent dizziness, fatigue
- Dry mouth, nasal congestion
- Dose-dependent weight gain
- May increase risk for diabetes and dyslipidemia
- Dose-dependent tachycardia
- Rare tardive dyskinesia (much reduced risk compared to conventional antipsychotics)



Life-Threatening or Dangerous Side Effects

- Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking atypical antipsychotics
- Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis
- Rare neuroleptic malignant syndrome (much reduced risk compared to conventional antipsychotics)
- Rare seizures

Weight Gain



- Many experience and/or can be significant in amount
- May be less than for some antipsychotics, more than for others

Sedation



- Many experience and/or can be significant in amount

What to Do About Side Effects

- Wait
- Wait
- Wait
- Anticholinergics may reduce motor side effects when present
- Weight loss, exercise programs, and medical management for high BMIs, diabetes, dyslipidemia
- Switch to another atypical antipsychotic

Best Augmenting Agents for Side Effects

- Benztrapine or trihexyphenidyl for motor side effects
- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 12–24 mg/day in 2 divided doses

Dosage Forms

- Tablet 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg

How to Dose

- Initial 2 mg in 2 divided doses on day 1; 4 mg in 2 divided doses on day 2; 8 mg in 2 divided doses on day 3; 12 mg in 2 divided doses on day 4; 16 mg in 2 divided doses on day 5; 20 mg in 2 divided doses on day 6; 24 mg in 2 divided doses on day 7
- Maximum dose studied is 32 mg/day



Dosing Tips

- May titrate even slower in patients who develop side effects, especially orthostasis, or when adding or switching from another drug with alpha 1 antagonist properties
- Patients most vulnerable to side effects during titration would be those sensitive to orthostasis (e.g., the young, the elderly, those with cardiovascular problems, those taking concomitant vasoactive drugs)
- Slow dosing could lead to delayed onset of antipsychotic effects
- Once daily use seems theoretically possible because the half-life of iloperidone is 18–33 hours
- Some patients may respond to doses greater than 24 mg/day if tolerated
- Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³
- If treatment is discontinued for more than 3 days, it may need to be restarted following the initial titration schedule in order to maximize tolerability
- Iloperidone should be discontinued in patients with persistent QTc measurements of more than 500 msec

Overdose

- Sedation, tachycardia, hypotension

Long-Term Use

- Not studied, but long-term maintenance treatment is often necessary for schizophrenia

Habit Forming

- No

How to Stop

- Down-titration, especially when simultaneously beginning a new antipsychotic while switching (i.e., cross-titration)
- Rapid discontinuation could theoretically lead to rebound psychosis and worsening of symptoms

Pharmacokinetics

- Half-life 18–33 hours
- Metabolized by CYP450 2D6 and 3A4
- Food does not affect absorption



Drug Interactions

- May increase effects of antihypertensive agents
- May antagonize levodopa, dopamine agonists
- May enhance QTc prolongation of other drugs capable of prolonging QTc interval
- Inhibitors of CYP450 2D6 (e.g., paroxetine, fluoxetine, duloxetine, quinidine) may increase plasma levels of iloperidone and require a dosage reduction by one-half of iloperidone
- Inhibitors of CYP450 3A4 (e.g., nefazodone, fluvoxamine, fluoxetine, ketoconazole) may increase plasma levels of iloperidone and require a dosage reduction by one-half of iloperidone



Other Warnings/ Precautions

- Use with caution in patients with conditions that predispose to hypotension (dehydration, overheating)
- Dysphagia has been associated with antipsychotic use, and iloperidone should be used cautiously in patients at risk for aspiration pneumonia
- Iloperidone prolongs QTc interval more than some other antipsychotics, an effect that is augmented by concomitant use of drugs that inhibit iloperidone metabolism
- Priapism has been reported with iloperidone

Do Not Use

- If patient is taking agents capable of significantly prolonging QTc interval (e.g., pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin)

- If there is a history of QTc prolongation or cardiac arrhythmia, recent acute myocardial infarction, uncompensated heart failure
- If there is a proven allergy to iloperidone

SPECIAL POPULATIONS

Renal Impairment

- Dose adjustment not generally necessary

Hepatic Impairment

- Not recommended for patients with hepatic impairment

Cardiac Impairment

- Drug should be used with caution because of risk of orthostatic hypotension
- Not recommended for patients with significant cardiovascular illness

Elderly

- Some patients may tolerate lower doses better
- Although atypical antipsychotics are commonly used for behavioral disturbances in dementia, no agent has been approved for treatment of elderly patients with dementia-related psychosis
- Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo, and also have an increased risk of cerebrovascular events



Children and Adolescents

- Safety and efficacy have not been established
- Children and adolescents using iloperidone may need to be monitored more often than adults



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be

- phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- There is a risk of abnormal muscle movements and withdrawal symptoms in newborns whose mothers took an antipsychotic during the third trimester; symptoms may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty feeding
- Psychotic symptoms may worsen during pregnancy and some form of treatment may be necessary
- Iloperidone may be preferable to anticonvulsant mood stabilizers if treatment is required during pregnancy
- National Pregnancy Registry for Atypical Antipsychotics: 1-866-961-2388 or <http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/>

Breast Feeding

- Unknown if iloperidone is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- ★ Recommended either to discontinue drug or bottle feed**
- Infants of women who choose to breast feed while on iloperidone should be monitored for possible adverse effects

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Some cases of psychosis and bipolar disorder refractory to treatment with other antipsychotics
- Patients wishing to avoid EPS

Potential Disadvantages

- Patients requiring rapid onset of antipsychotic action without dosage titration
- Patients noncompliant with twice daily dosing
- Cognitive symptoms

- Unstable mood (both depression and mania)
- Aggressive symptoms

Primary Target Symptoms

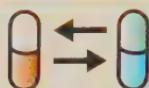
- Positive symptoms of psychosis
- Negative symptoms of psychosis



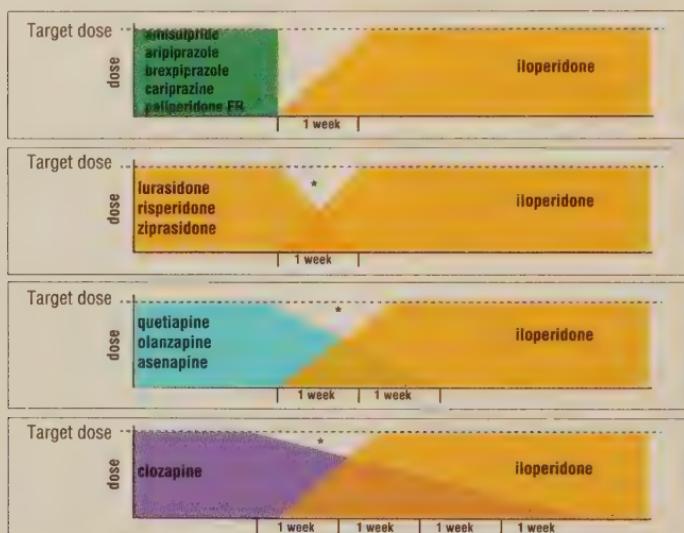
Pearls

- Not approved for mania, but all atypical antipsychotics approved for acute treatment of schizophrenia have proven effective in the acute treatment of mania as well
- Seems to have placebo-level EPS, including little or no akathisia
- Potent alpha 1 blocking properties suggest potential utility in PTSD (e.g., nightmares, as for prazosin)
- Binding properties suggest theoretical efficacy in depression, but studies and clinical experience are required to confirm this
- QTc warning similar to that for ziprasidone, where this has not materialized into a significant clinical problem
- A 4-week depot preparation is in clinical testing
- Early studies indicate iloperidone's efficacy may be linked to pharmacogenomic markers such as ciliary neurotrophic factor (CNTF), and others
- Patients with inadequate responses to atypical antipsychotics may benefit from determination of plasma drug levels and, if low, a dosage increase even beyond the usual prescribing limits
- For treatment-resistant patients, especially those with impulsivity, aggression, violence, and self-harm, long-term polypharmacy with 2 atypical antipsychotics or with 1 atypical antipsychotic and 1 conventional antipsychotic may be useful or even necessary while closely monitoring
- In such cases, it may be beneficial to combine 1 depot antipsychotic with 1 oral antipsychotic

THE ART OF SWITCHING

**Switching from Oral Antipsychotics to Iloperidone**

- With aripiprazole, amisulpride, and paliperidone ER, immediate stop is possible
- Clinical experience has shown that quetiapine, olanzapine, and asenapine should be tapered off slowly over a period of 3–4 weeks, to allow patients to readapt to the withdrawal of blocking cholinergic, histaminergic, and alpha-1 receptors
- Clozapine should always be tapered off slowly, over a period of 4 weeks or more
- Benzodiazepine or anticholinergic medication can be administered during cross-titration to help alleviate side effects such as insomnia, agitation, and/or psychosis

**Suggested Reading**

Albers LJ, Musenga A, Raggi MA. Iloperidone: a new benzisoxazole atypical antipsychotic drug. Is it novel enough to impact the crowded atypical antipsychotic market? *Expert Opin Investig Drugs* 2008;17:61–75.

Citrome L. Iloperidone for schizophrenia: a review of the efficacy and safety profile for this newly commercialized second-generation antipsychotics. *Int J Clin Pract* 2009;63:1237–48.

Kane JM, Lauriello J, Laska E, Di Marino M, Wolfgang CD. Long-term efficacy and safety

of iloperidone: results from 3 clinical trials for the treatment of schizophrenia. *J Clin Psychopharmacol* 2008;28(2 Suppl 1):S29–35.

Tarazi F, Stahl SM. Iloperidone, asenapine and lurasidone: a primer on their current status. *Exp Opin Pharmacother* 2012;13(13):1911–22.

Volpi S, Potkin SG, Malhotra AK, Licamele L, Lavedan C. Applicability of a genetic signature for enhanced iloperidone efficacy in the treatment of schizophrenia. *J Clin Psychiatry* 2009;70:801–9.

THERAPEUTICS

Brands • Tofranil

see index for additional brand names

Generic? Yes**Class**

- Neuroscience-based Nomenclature: serotonin norepinephrine reuptake inhibitor (SN-RI)
- Tricyclic antidepressant (TCA)
- Serotonin and norepinephrine/noradrenaline reuptake inhibitor

Commonly Prescribed for

(bold for FDA approved)

• Depression**• Enuresis****• Anxiety****• Insomnia****• Neuropathic pain/chronic pain****• Treatment-resistant depression****• Cataplexy syndrome****How the Drug Works**

- Boosts neurotransmitters serotonin and norepinephrine/noradrenaline
- Blocks serotonin reuptake pump (serotonin transporter), presumably increasing serotonergic neurotransmission
- Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing noradrenergic neurotransmission
- Presumably desensitizes both serotonin 1A receptors and beta adrenergic receptors
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, imipramine can increase dopamine neurotransmission in this part of the brain
- May be effective in treating enuresis because of its anticholinergic properties

How Long Until It Works

- May have immediate effects in treating insomnia or anxiety
- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all

- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment of depression is complete remission of current symptoms as well as prevention of future relapses
- The goal of treatment of chronic neuropathic pain is to reduce symptoms as much as possible, especially in combination with other treatments
- Treatment of depression most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Treatment of chronic neuropathic pain may reduce symptoms, but rarely eliminates them completely, and is not a cure since symptoms can recur after medicine is stopped
- Continue treatment of depression until all symptoms are gone (remission)
- Once symptoms of depression are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders and chronic pain may also need to be indefinite, but long-term treatment is not well studied in these conditions

If It Doesn't Work

- Many depressed patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other depressed patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer



Best Augmenting Combos for Partial Response or Treatment Resistance

- Lithium, buspirone, thyroid hormone (for depression)
- Gabapentin, tiagabine, other anticonvulsants, even opiates if done by experts while monitoring carefully in difficult cases (for chronic pain)

Tests

- Baseline EKG is recommended for patients over age 50
- Since tricyclic and tetracyclic antidepressants are frequently associated with weight gain, before starting treatment, weigh all patients and determine if the patient is already overweight (BMI 25.0–29.9) or obese (BMI ≥30)
- Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–125 mg/dL), diabetes (fasting plasma glucose >126 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management
- Monitor weight and BMI during treatment
- While giving a drug to a patient who has gained >5% of initial weight, consider evaluating for the presence of pre-diabetes, diabetes, or dyslipidemia, or consider switching to a different antidepressant
- EKGs may be useful for selected patients (e.g., those with personal or family history of QTc prolongation; cardiac arrhythmia; recent myocardial infarction; uncompensated heart failure; or taking agents that prolong QTc interval such as pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin, etc.)
- Patients at risk for electrolyte disturbances (e.g., patients on diuretic therapy) should have baseline and periodic serum potassium and magnesium measurements

SIDE EFFECTS

How Drug Causes Side Effects

- Anticholinergic activity may explain sedative effects, dry mouth, constipation, and blurred vision
- Sedative effects and weight gain may be due to antihistamine properties
- Blockade of alpha adrenergic 1 receptors may explain dizziness, sedation, and hypotension
- Cardiac arrhythmias and seizures, especially in overdose, may be caused by blockade of ion channels

Notable Side Effects

- Blurred vision, constipation, urinary retention, increased appetite, dry mouth, nausea, diarrhea, heartburn, unusual taste in mouth, weight gain
- Fatigue, weakness, dizziness, sedation, headache, anxiety, nervousness, restlessness
- Sexual dysfunction, sweating



Life-Threatening or Dangerous Side Effects

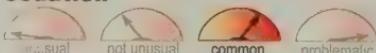
- Paralytic ileus, hyperthermia (TCAs + anticholinergic agents)
- Lowered seizure threshold and rare seizures
- Orthostatic hypotension, sudden death, arrhythmias, tachycardia
- QTc prolongation
- Hepatic failure, extrapyramidal symptoms
- Increased intraocular pressure, increased psychotic symptoms
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Many experience and/or can be significant in amount
- Can increase appetite and carbohydrate craving

Sedation



- Many experience and/or can be significant in amount
- Tolerance to sedative effects may develop with long-term use

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- Switch to an SSRI or newer antidepressant

Best Augmenting Agents for Side Effects

- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 50–150 mg/day

Dosage Forms

- Capsule 75 mg, 100 mg, 125 mg, 150 mg
- Tablet 10 mg, 25 mg, 50 mg

How to Dose

- Initial 25 mg/day at bedtime; increase by 25 mg every 3–7 days
- 75–100 mg/day once daily or in divided doses; gradually increase daily dose to achieve desired therapeutic effects; dose at bedtime for daytime sedation and in morning for insomnia; maximum dose 300 mg/day



Dosing Tips

- If given in a single dose, should generally be administered at bedtime because of its sedative properties
- If given in split doses, largest dose should generally be given at bedtime because of its sedative properties
- If patients experience nightmares, split dose and do not give large dose at bedtime
- Patients treated for chronic pain may only require lower doses
- Tofranil-PM(r) (imipramine pamoate) 100- and 125-mg capsules contain the dye tartrazine (FD&C yellow No. 5), which may cause allergic reactions in some patients; this reaction is more likely in patients with sensitivity to aspirin.

- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar disorder, and switch to a mood stabilizer or an atypical antipsychotic

Overdose

- Death may occur; convulsions, cardiac dysrhythmias, severe hypotension, CNS depression, coma, changes in EKG

Long-Term Use

- Safe

Habit Forming

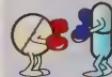
- No

How to Stop

- Taper to avoid withdrawal effects
- Even with gradual dose reduction some withdrawal symptoms may appear within the first 2 weeks
- Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation
- If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly

Pharmacokinetics

- Substrate for CYP450 2D6 and 1A2
- Metabolized to an active metabolite, desipramine, a predominantly norepinephrine reuptake inhibitor, by demethylation via CYP450 1A2
- Food does not affect absorption



Drug Interactions

- Tramadol increases the risk of seizures in patients taking TCAs
- Use of TCAs with anticholinergic drugs may result in paralytic ileus or hyperthermia
- Fluoxetine, paroxetine, bupropion, duloxetine, and other CYP450 2D6 inhibitors may increase TCA concentrations
- Fluvoxamine, a CYP450 1A2 inhibitor, can decrease the conversion of imipramine to desmethylimipramine (desipramine) and increase imipramine plasma concentrations
- Cimetidine may increase plasma concentrations of TCAs and cause anticholinergic symptoms

- Phenothiazines or haloperidol may raise TCA blood concentrations
- May alter effects of antihypertensive drugs; may inhibit hypotensive effects of clonidine
- Use with sympathomimetic agents may increase sympathetic activity
- Methylphenidate may inhibit metabolism of TCAs
- Activation and agitation, especially following switching or adding antidepressants, may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of imipramine



Other Warnings/ Precautions

- Add or initiate other antidepressants with caution for up to 2 weeks after discontinuing imipramine
- Generally, do not use with MAO inhibitors, including 14 days after MAOIs are stopped; do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing imipramine, but see Pearls
- Use with caution in patients with history of seizure, urinary retention, angle-closure glaucoma, hyperthyroidism
- TCAs can increase QTc interval, especially at toxic doses, which can be attained not only by overdose but also by combining with drugs that inhibit its metabolism via CYP450 2D6, potentially causing torsade de pointes-type arrhythmia or sudden death
- Because TCAs can prolong QTc interval, use with caution in patients who have bradycardia or who are taking drugs that can induce bradycardia (e.g., beta blockers, calcium channel blockers, clonidine, digitalis)
- Because TCAs can prolong QTc interval, use with caution in patients who have hypokalemia and/or hypomagnesemia or who are taking drugs that can induce hypokalemia and/or magnesemia (e.g., diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactide)
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of

- nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is recovering from myocardial infarction
- If patient is taking agents capable of significantly prolonging QTc interval (e.g., pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin)
- If there is a history of QTc prolongation or cardiac arrhythmia, recent acute myocardial infarction, uncompensated heart failure
- If patient is taking drugs that inhibit TCA metabolism, including CYP450 2D6 inhibitors, except by an expert
- If there is reduced CYP450 2D6 function, such as patients who are poor 2D6 metabolizers, except by an expert and at low doses
- If there is a proven allergy to imipramine, desipramine, or lofepramine

SPECIAL POPULATIONS

Renal Impairment

- Cautious use; may need lower dose

Hepatic Impairment

- Cautious use; may need lower dose

Cardiac Impairment

- Baseline EKG is recommended
- TCAs have been reported to cause arrhythmias, prolongation of conduction time, orthostatic hypotension, sinus tachycardia, and heart failure, especially in the diseased heart
- Myocardial infarction and stroke have been reported with TCAs
- TCAs produce QTc prolongation, which may be enhanced by the existence of bradycardia, hypokalemia, congenital or acquired long QTc interval, which should be evaluated prior to administering imipramine

- Use with caution if treating concomitantly with a medication likely to produce prolonged bradycardia, hypokalemia, slowing of intracardiac conduction, or prolongation of the QTc interval
 - Avoid TCAs in patients with a known history of QTc prolongation, recent acute myocardial infarction, and uncompensated heart failure
 - TCAs may cause a sustained increase in heart rate in patients with ischemic heart disease and may worsen (decrease) heart rate variability, an independent risk of mortality in cardiac populations
 - Since SSRIs may improve (increase) heart rate variability in patients following a myocardial infarct and may improve survival as well as mood in patients with acute angina or following a myocardial infarction, these are more appropriate agents for cardiac population than tricyclic/tetracyclic antidepressants
- * Risk/benefit ratio may not justify use of TCAs in cardiac impairment**

Elderly

- Baseline EKG is recommended for patients over age 50
- May be more sensitive to anticholinergic, cardiovascular, hypotensive, and sedative effects
- Initial 30–40 mg/day; maximum dose 100 mg/day
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Used age 6 and older for enuresis; age 12 and older for other disorders

- Several studies show lack of efficacy of TCAs for depression
- May be used to treat hyperactive/impulsive behaviors
- Some cases of sudden death have occurred in children taking TCAs
- Adolescents: initial 30–40 mg/day; maximum 100 mg/day
- Children: initial 1.5 mg/kg per day; maximum 5 mg/kg per day
- Functional enuresis: 50 mg/day (age 6–12) or 75 mg/day (over 12)



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Crosses the placenta
- Should be used only if potential benefits outweigh potential risks
- Adverse effects have been reported in infants whose mothers took a TCA (lethargy, withdrawal symptoms, fetal malformations)
- Evaluate for treatment with an antidepressant with a better risk/benefit ratio

Breast Feeding

- Some drug is found in mother's breast milk
- * Recommended either to discontinue drug or bottle feed**
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY**Potential Advantages**

- Patients with insomnia
- Severe or treatment-resistant depression
- Patients with enuresis

Potential Disadvantages

- Pediatric and geriatric patients
- Patients concerned with weight gain
- Cardiac patients

Primary Target Symptoms

- Depressed mood
- Chronic pain

**Pearls**

- Was once one of the most widely prescribed agents for depression
- **Probably the most preferred TCA for treating enuresis in children**
- **Preference of some prescribers for imipramine over other TCAs for the treatment of enuresis is based more upon art and anecdote and empiric clinical experience than comparative clinical trials with other TCAs**
- TCAs are no longer generally considered a first-line treatment option for depression because of their side effect profile
- TCAs may aggravate psychotic symptoms
- Alcohol should be avoided because of additive CNS effects
- Underweight patients may be more susceptible to adverse cardiovascular effects
- Children, patients with inadequate hydration, and patients with cardiac disease may be more susceptible to TCA-induced cardiotoxicity than healthy adults
- For the expert only: although generally prohibited, a heroic but potentially dangerous treatment for severely treatment-resistant patients is to give a

tricyclic/tetracyclic antidepressant other than clomipramine simultaneously with an MAOI for patients who fail to respond to numerous other antidepressants

- If this option is elected, start the MAOI with the tricyclic/tetracyclic antidepressant simultaneously at low doses after appropriate drug washout, then alternately increase doses of these agents every few days to a week as tolerated
- Although very strict dietary and concomitant drug restrictions must be observed to prevent hypertensive crises and serotonin syndrome, the most common side effects of MAOI/tricyclic or tetracyclic combinations may be weight gain and orthostatic hypotension
- Patients on TCAs should be aware that they may experience symptoms such as photosensitivity or blue-green urine
- SSRIs may be more effective than TCAs in women, and TCAs may be more effective than SSRIs in men
- Since tricyclic/tetracyclic antidepressants are substrates for CYP450 2D6, and 7% of the population (especially Caucasians) may have a genetic variant leading to reduced activity of 2D6, such patients may not safely tolerate normal doses of tricyclic/tetracyclic antidepressants and may require dose reduction
- Phenotypic testing may be necessary to detect this genetic variant prior to dosing with a tricyclic/tetracyclic antidepressant, especially in vulnerable populations such as children, elderly, cardiac populations, and those on concomitant medications
- Patients who seem to have extraordinarily severe side effects at normal or low doses may have this phenotypic CYP450 2D6 variant and require low doses or switching to another antidepressant not metabolized by 2D6



Suggested Reading

- Anderson IM. Meta-analytical studies on new antidepressants. *Br Med Bull* 2001;57:161–78.
- Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *J Aff Disorders* 2000;58:19–36.
- Preskorn SH. Comparison of the tolerability of bupropion, fluoxetine, imipramine, nefazodone, paroxetine, sertraline, and venlafaxine. *J Clin Psychiatry* 1995;56(Suppl 6):S12–21.
- Workman EA, Short DD. Atypical antidepressants versus imipramine in the treatment of major depression: a meta-analysis. *J Clin Psychiatry* 1993;54:5–12.

THERAPEUTICS

Brands

• Marplan
see index for additional brand names

Generic?

Not in USA



Class

- Neuroscience-based Nomenclature: serotonin, norepinephrine, dopamine enzyme inhibitor (SN-EI)
- Monoamine oxidase inhibitor (MAOI)

Commonly Prescribed for

(bold for FDA approved)

- **Depression**
- Treatment-resistant depression
- Treatment-resistant panic disorder
- Treatment-resistant social anxiety disorder



How the Drug Works

- Irreversibly blocks monoamine oxidase (MAO) from breaking down norepinephrine, serotonin, and dopamine
- This presumably boosts noradrenergic, serotonergic, and dopaminergic neurotransmission

How Long Until It Works

- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Continue treatment until all symptoms are gone (remission)
- Once symptoms are gone, continue treating for 1 year for the first episode of depression

- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders may also need to be indefinite

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some patients who have an initial response may relapse even though they continue treatment, sometimes called “poop-out”
- Consider increasing dose, switching to another agent, or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer



Best Augmenting Combos for Partial Response or Treatment Resistance

- *** Augmentation of MAOIs has not been systematically studied, and this is something for the expert, to be done with caution and with careful monitoring**
- *** A stimulant such as d-amphetamine or methylphenidate (with caution; may activate bipolar disorder and suicidal ideation; may elevate blood pressure)**
- Lithium
- Mood-stabilizing anticonvulsants
- Atypical antipsychotics (with special caution for those agents with monoamine reuptake blocking properties, such as ziprasidone and zotepine)

Tests

- Patients should be monitored for changes in blood pressure
- Patients receiving high doses or long-term treatment should have hepatic function evaluated periodically

- ✿ Since MAOIs are frequently associated with weight gain, before starting treatment, weigh all patients and determine if the patient is already overweight (BMI 25.0–29.9) or obese (BMI ≥30)
- Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–125 mg/dL), diabetes (fasting plasma glucose >126 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management
- ✿ Monitor weight and BMI during treatment
- ✿ While giving a drug to a patient who has gained >5% of initial weight, consider evaluating for the presence of pre-diabetes, diabetes, or dyslipidemia, or consider switching to a different antidepressant

SIDE EFFECTS

How Drug Causes Side Effects

- Theoretically due to increases in monoamines in parts of the brain and body and at receptors other than those that cause therapeutic actions (e.g., unwanted actions of serotonin in sleep centers causing insomnia, unwanted actions of norepinephrine on vascular smooth muscle causing hypertension, etc.)
- Side effects are generally immediate, but immediate side effects often disappear in time

Notable Side Effects

- Dizziness, sedation, headache, sleep disturbances, fatigue, weakness, tremor, movement problems, blurred vision, increased sweating
- Constipation, dry mouth, nausea, change in appetite, weight gain
- Sexual dysfunction
- Orthostatic hypotension (dose-related); syncope may develop at high doses



Life-Threatening or Dangerous Side Effects

- Hypertensive crisis (especially when MAOIs are used with certain tyramine-containing foods or prohibited drugs)
- Induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)
- Seizures
- Hepatotoxicity

Weight Gain



- Many experience and/or can be significant in amount

Sedation



- Many experience and/or can be significant in amount
- Can also cause activation

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- Take at night if daytime sedation
- Switch after appropriate washout to an SSRI or newer antidepressant

Best Augmenting Agents for Side Effects

- Trazodone (with caution) for insomnia
- Benzodiazepines for insomnia
- ✿ Single oral or sublingual dose of a calcium channel blocker (e.g., nifedipine) for urgent treatment of hypertension due to drug interaction or dietary tyramine
- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 40–60 mg/day

Dosage Forms

- Tablet 10 mg

How to Dose

- Initial 10 mg twice a day; increase by 10 mg/day every 2–4 days; dosed 2–4 times/day; maximum dose 60 mg/day



Dosing Tips

- Orthostatic hypotension, especially at high doses, may require splitting into 3 or 4 daily doses
- Patients receiving high doses may need to be evaluated periodically for effects on the liver
- Little evidence to support efficacy of isocarboxazid at doses below 30 mg/day

Overdose

- Dizziness, sedation, ataxia, headache, insomnia, restlessness, anxiety, irritability, cardiovascular effects, confusion, respiratory depression, or coma may also occur

Long-Term Use

- May require periodic evaluation of hepatic function
- MAOIs may lose some efficacy long-term

Habit Forming

- Some patients have developed dependence to MAOIs

How to Stop

- Generally no need to taper, as drug wears off slowly over 2–3 weeks

Pharmacokinetics

- Clinical duration of action may be up to 14 days due to irreversible enzyme inhibition



Drug Interactions

- Tramadol may increase the risk of seizures in patients taking an MAOI
- Can cause a fatal “serotonin syndrome” when combined with drugs that block serotonin reuptake, so do not use with a serotonin reuptake inhibitor or for 5 half-lives after stopping the serotonin reuptake inhibitor (see Table 1 after Pearls)

- Hypertensive crisis with headache, intracranial bleeding, and death may result from combining MAOIs with sympathomimetic drugs (e.g., amphetamines, methylphenidate, cocaine, dopamine, epinephrine, norepinephrine, and related compounds methyldopa, levodopa, L-tryptophan, L-tyrosine, and phenylalanine)

- Do not combine with another MAOI, alcohol, or guanethidine
- Adverse drug reactions can result from combining MAOIs with tricyclic/tetracyclic antidepressants and related compounds, including carbamazepine, cyclobenzaprine, and mirtazapine, and should be avoided except by experts to treat difficult cases (see Pearls)
- MAOIs in combination with spinal anesthesia may cause combined hypotensive effects
- Combination of MAOIs and CNS depressants may enhance sedation and hypotension



Other Warnings/ Precautions

- Use requires low tyramine diet (see Table 2 after Pearls)
- Patient and prescriber must be vigilant to potential interactions with any drug, including antihypertensives and over-the-counter cough/cold preparations
- Over-the-counter medications to avoid include cough and cold preparations, including those containing dextromethorphan, nasal decongestants (tablets, drops, or spray), hay-fever medications, sinus medications, asthma inhalant medications, anti-appetite medications, weight reducing preparations, “pep” pills (see Table 3 after Pearls)
- Use cautiously in patients receiving reserpine, anesthetics, disulfiram, metrizamide, anticholinergic agents
- Isocarboxazid is not recommended for use in patients who cannot be monitored closely
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart

- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is taking meperidine (pethidine)
- If patient is taking a sympathomimetic agent or taking guanethidine
- If patient is taking another MAOI
- If patient is taking any agent that can inhibit serotonin reuptake (e.g., SSRIs, sibutramine, tramadol, milnacipran, duloxetine, venlafaxine, clomipramine, etc.)
- If patient is taking diuretics, dextromethorphan
- If patient has pheochromocytoma
- If patient has cardiovascular or cerebrovascular disease
- If patient has frequent or severe headaches
- If patient is undergoing elective surgery and requires general anesthesia
- If patient has a history of liver disease or abnormal liver function tests
- If patient is taking a prohibited drug
- If patient is not compliant with a low tyramine diet
- If there is a proven allergy to isocarboxazid

SPECIAL POPULATIONS

Renal Impairment

- Use with caution – drug may accumulate in plasma
- May require lower than usual adult dose

Hepatic Impairment

- Not for use in hepatic impairment

Cardiac Impairment

- Contraindicated in patients with congestive heart failure or hypertension
- Any other cardiac impairment may require lower than usual adult dose
- Patients with angina pectoris or coronary artery disease should limit their exertion

Elderly

- Initial dose lower than usual adult dose

- Elderly patients may have greater sensitivity to adverse effects
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Not recommended for use in children under age 16
- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLL or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester
- Should evaluate patient for treatment with an antidepressant with a better risk/benefit ratio

Breast Feeding

- Some drug is found in mother's breast milk
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late

in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period

- Should evaluate patient for treatment with an antidepressant with a better risk/benefit ratio

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Atypical depression
- Severe depression
- Treatment-resistant depression or anxiety disorders

Potential Disadvantages

- Requires compliance to dietary restrictions, concomitant drug restrictions
- Patients with cardiac problems or hypertension
- Multiple daily doses

Primary Target Symptoms

- Depressed mood
- Somatic symptoms
- Sleep and eating disturbances
- Psychomotor retardation
- Morbid preoccupation



Pearls

- MAOIs are generally reserved for second-line use after SSRIs, SNRIs, and combinations of newer antidepressants have failed
- Despite little utilization, some patients respond to isocarboxazid who do not respond to other antidepressants including other MAOIs
- Patient should be advised not to take any prescription or over-the-counter drugs without consulting their doctor because of possible drug interactions with the MAOI
- Headache is often the first symptom of hypertensive crisis
- The rigid dietary restrictions may reduce compliance (see Table 2 after Pearls)
- Mood disorders can be associated with eating disorders (especially in adolescent

females), and isocarboxazid can be used to treat both depression and bulimia

- MAOIs are a viable second-line treatment option in depression, but are not frequently used

• Myths about the danger of dietary tyramine can be exaggerated, but prohibitions against concomitant drugs often not followed closely enough

- Orthostatic hypotension, insomnia, and sexual dysfunction are often the most troublesome common side effects

• MAOIs should be for the expert, especially if combining with agents of potential risk (e.g., stimulants, trazodone, TCAs)

• MAOIs should not be neglected as therapeutic agents for the treatment-resistant

- Although generally prohibited, a heroic but potentially dangerous treatment for severely treatment-resistant patients is for an expert to give a tricyclic/tetracyclic antidepressant other than clomipramine simultaneously with an MAOI for patients who fail to respond to numerous other antidepressants

- Use of MAOIs with clomipramine is always prohibited because of the risk of serotonin syndrome and death

• Amoxapine may be the preferred tricyclic/tetracyclic antidepressant to combine with an MAOI in heroic cases due to its theoretically protective 5HT2A antagonist properties

- If this option is elected, start the MAOI with the tricyclic/tetracyclic antidepressant simultaneously at low doses after appropriate drug washout, then alternately increase doses of these agents every few days to a week as tolerated

• Although very strict dietary and concomitant drug restrictions must be observed to prevent hypertensive crises and serotonin syndrome, the most common side effects of MAOI and tricyclic/tetracyclic combinations may be weight gain and orthostatic hypotension

ISOCARBOXAZID (continued)

Table 1. Drugs contraindicated due to risk of serotonin syndrome/toxicity

Do Not Use:			
Antidepressants	Drugs of Abuse	Opioids	Other
SSRIs	MDMA (ecstasy)	Meperidine	Non-subcutaneous sumatriptan
SNRIs	Cocaine	Tramadol	Chlorpheniramine
Clomipramine	Methamphetamine	Methadone	Brompheniramine
St. John's wort	High-dose or injected amphetamine	Fentanyl	Dextromethorphan
			Procarbazine?

Table 2. Dietary guidelines for patients taking MAOIs

Foods to avoid*	Foods allowed
Dried, aged, smoked, fermented, spoiled, or improperly stored meat, poultry, and fish	Fresh or processed meat, poultry, and fish; properly stored pickled or smoked fish
Broad bean pods	All other vegetables
Aged cheeses	Processed cheese slices, cottage cheese, ricotta cheese, yogurt, cream cheese
Tap and unpasteurized beer	Canned or bottled beer and alcohol
Marmite	Brewer's and baker's yeast
Sauerkraut, kimchee	
Soy products/tofu	Peanuts
Banana peel	Bananas, avocados, raspberries
Tyramine-containing nutritional supplement	

*Not necessary for 6-mg transdermal or low-dose oral selegiline

Table 3. Drugs that boost norepinephrine: should only be used with caution with MAOIs

Use With Caution:			
Decongestants	Stimulants	Antidepressants with norepinephrine reuptake inhibition	Other
Phenylephrine	Amphetamines	Most tricyclics	Phentermine
Pseudoephedrine	Methylphenidate	NRIs	Local anesthetics containing vasoconstrictors
	Cocaine	NDRIs	
	Methamphetamine		
	Modafinil		Tapentadol
	Armodafinil		



Suggested Reading

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Lippman SB, Nash K. Monoamine oxidase inhibitor update. Potential adverse food and drug interactions. *Drug Saf* 1990;5:195-204.

THERAPEUTICS

Brands

Ketalar
see index for additional brand names

Generic? Yes**Class**

- N-methyl-D-aspartate (NMDA) receptor antagonist

Commonly Prescribed for

(bold for FDA approved)

- **Induction and maintenance of general anesthesia**
- Pain/neuropathic pain
- Sedation
- Treatment-resistant depression (experimental)

**How the Drug Works**

- Ketamine is a noncompetitive open channel inhibitor of the NMDA receptor; specifically, it binds to the phencyclidine site of the NMDA receptor
- This leads to downstream glutamate release and consequent stimulation of other glutamate receptors, including AMPA receptors
- Theoretically, ketamine may have antidepressant effects at low (subanesthetic) doses because activation of AMPA receptors leads to activation of signal transduction cascades that cause the expression of synaptic proteins and an increase in the density of dendritic spines
- Low (subanesthetic) doses also produce analgesia and modulate central sensitization, hyperalgesia, and opioid tolerance

How Long Until It Works

- For treatment-resistant depression, antidepressant effects can occur within hours
- For neuropathic pain, effects can occur within hours but may take weeks for full effect

If It Works

- For treatment-resistant depression, can immediately alleviate depressed mood and suicidal ideation, but antidepressant effects last only a few days

- For neuropathic pain, can continue to use as long as it is beneficial

If It Doesn't Work

- Try a traditional antidepressant or electroconvulsive therapy (ECT) for treatment-resistant depression
- Try traditional analgesics and treatments for neuropathic pain

**Best Augmenting Combos for Partial Response or Treatment Resistance**

- For neuropathic pain, may use cautiously with opioids
- For treatment-resistant depression, combinations have not been systematically studied

Tests

- None for healthy individuals

SIDE EFFECTS

How Drug Causes Side Effects

- Direct effect on NMDA receptors

Notable Side Effects

- When used as an anesthesia induction/maintenance agent (generally at doses >2 mg/kg IV), it may produce emergent psychosis, including auditory and visual hallucinations, restlessness, disorientation, vivid dreams, and irrational behavior. Spontaneous involuntary movements, nystagmus, hypertonus, and vocalizations are also common. These adverse effects are uncommon with very low-dose therapy.
- CSF pressure increased, erythema (transient), morbilliform rash (transient), anorexia, pain/erythema at the injection site, exanthema at the injection site, skeletal muscle tone enhanced, intraocular pressure increased, bronchial secretions increased, potential for dependence with prolonged use, emergence reactions (includes confusion, dreamlike state, excitement, irrational behavior, vivid imagery)
- Psychotomimetic phenomena (euphoria, dysphasia, blunted affect, psychomotor retardation, vivid dreams, nightmares,

impaired attention, memory and judgment, illusions, hallucinations, altered body image), delirium, dizziness, diplopia, blurred vision, nystagmus, altered hearing, hypertension, tachycardia, hypersalivation, nausea and vomiting, erythema and pain at injection site

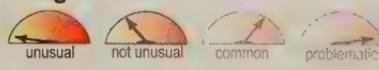
- Urinary tract toxicity
- When used at higher doses in anesthesia, tonic-clonic movements are very common (>10%); however, these have not been reported after oral use or with the lower parenteral doses used for analgesia



Life-Threatening or Dangerous Side Effects

- Syncope or cardiac arrhythmias
- Hypertension/hypotension
- Anaphylaxis
- CNS depression
- Respiratory depression/apnea
- Airway obstruction/laryngospasm

Weight Gain



- Reported but not expected

Sedation



- Many experience and/or can be significant in amount

What to Do About Side Effects

- Pretreatment with a benzodiazepine reduces incidence of psychosis by >50%
- For CNS side effects, discontinuation of nonessential centrally acting medications may help

Best Augmenting Agents for Side Effects

- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- Oral: 10–50 mg
- IV infusion: 1–10 µg/kg per minute

Dosage Forms

- Oral solution: 50 mg/mL
- Injection: 50 mg/mL

How to Dose

- For pain (oral): initial 10 mg; titrate up as appropriate
 - For pain (IM): 2–4 mg/kg
 - For pain (IV): 0.2–0.075 mg/kg
- For pain (continuous IV infusion): 2–7 µg/kg per minute



Dosing Tips

- Slow titration can reduce side effects
- Food does not affect absorption
- For oral use: to prepare 100 mL of 50 mg/5 mL ketamine oral solution
 - 2 x 10 mL vials of generic ketamine 50 mg/mL for injection (cheapest concentration)
 - 80 mL purified water
- Store in a refrigerator with an expiry date of 1 week from manufacture
- Patients can add their own flavoring, e.g., fruit cordial, just before use to disguise the bitter taste
- For sublingual use:
 - Place under the tongue and ask patient not to swallow for 2 minutes
 - Use a high concentration to minimize dose volume; retaining >2 mL is difficult
 - Start with 10 mg
- Incompatibility
 - Ketamine forms precipitates with barbiturates and diazepam (manufacturer's data on file); do not mix
 - Mixing lorazepam with ketamine is also not recommended; compatibility data are lacking, and there is a risk of adsorption of lorazepam to the tubing

Overdose

- Restlessness, psychosis, hallucinations, stupor

Long-Term Use

- Safe

Habit Forming

- No

How to Stop

- Taper not necessary

Pharmacokinetics

- Plasma half-life: alpha: 10–15 minutes; beta: 2.5 hours; 1–3 hours IM; 2.5–3 hours orally; 12 hours norketamine
- Metabolized by CYP450 2B6, 2C9, and 3A4



Drug Interactions

- Use with caution with other drugs that are NMDA antagonists (amantadine, memantine, dextromethorphan)
- Ketamine may increase the effects of other sedatives, including benzodiazepines, barbiturates, opioids, anesthetics, and alcohol
- CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole) can increase plasma concentrations of ketamine and reduce those of norketamine, but the clinical relevance of this is unclear
- Plasma concentrations of ketamine are increased by diazepam
- Barbiturates and hydroxyzine may increase the effects of ketamine; avoid combination



Other Warnings/ Precautions

- Use with caution in patients with current or past history of psychiatric disorder; epilepsy, glaucoma, hypertension, heart failure, ischemic heart disease, and a history of cerebrovascular accidents

Do Not Use

- If patient has a condition in which an increase in blood pressure would be hazardous
- If patient has schizophrenia or another psychotic disorder
- If patient has a condition in which an increase in intraocular pressure would be hazardous
- If there is a proven allergy to ketamine

SPECIAL POPULATIONS

Renal Impairment

- Reduce dose for moderate impairment
- Should not be used in severe impairment

Hepatic Impairment

- Dose reduction not necessary

Cardiac Impairment

- Use with caution

Elderly

- Some patients may tolerate lower doses better



Children and Adolescents

- Safety and efficacy have not been established



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Use only if potential benefits outweigh the potential risks to the fetus

Breast Feeding

- Unknown if ketamine is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- Recommended either to discontinue drug or bottle feed

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- For pain, may be especially useful when used in conjunction with opioids
- Severely treatment-resistant depression, suicidal ideation

Potential Disadvantages

- May produce dysphoria, nightmares, excitement (uncommon with very low-dose therapy)
- Antidepressant effects are short-lived

Primary Target Symptoms

- Pain
- Treatment-resistant depression



Pearls

- Actions in treatment-resistant depression are transient, lasting only a few days following infusion
- The use of ketamine can cause urinary tract symptoms (e.g., frequency, urgency, urge incontinence, dysuria, and hematuria); the causal agent has not been determined, but direct irritation by ketamine and/or its metabolites is a possibility. (Investigations have revealed interstitial cystitis, detrusor overactivity, decreased bladder capacity; symptoms generally settle several weeks after stopping ketamine.)
- May be used in combination with anticholinergic agents to decrease hypersalivation
- Do not mix with barbiturates or diazepam (precipitation may occur)
- Bronchodilation is beneficial in asthmatic or chronic obstructive pulmonary disease (COPD) patients. Laryngeal reflexes may remain intact or may be obtunded.
- The direct myocardial depressant action of ketamine can be seen in stressed, catecholamine-deficient patients

- Ketamine releases endogenous catecholamines (epinephrine, norepinephrine), which maintain blood pressure and heart rate, and increase myocardial oxygen demand
- Ketamine increases cerebral metabolism and cerebral blood flow while producing a noncompetitive block of the neuronal postsynaptic NMDA receptor
- Lowers seizure threshold
- Recent laboratory/clinical studies support the use of low-dose ketamine to improve postoperative analgesia/outcome
- May be especially beneficial for refractory neuropathic pain/complex regional pain syndrome
- May be especially beneficial when used in conjunction with opioids
- (S)-ketamine is available in a preservative-free solution in Europe; however, it currently is not approved by the FDA. S(+)-ketamine may be more potent and have fewer side effects when used intravenously than the racemate. Although not rigorously tested and not available in the USA; some European investigators have utilized the preservation-free solution for intrathecal/epidural use – this is not recommended



Suggested Reading

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pain syndrome: possible mechanisms. *Expert Rev Neurother* 2011;11(5):719–34.

Stahl SM. Mechanism of action of ketamine. *CNS Spectrums* 2013;18(4):171–4.

Zarate CA Jr, Singh JB, Carlson PH, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* 2006;63(8):856–64.

THERAPEUTICS

- Brands**
- Lamictal
 - Labileno
 - Lamictin

see index for additional brand names

Generic? Yes



Class

- Neuroscience-based Nomenclature: glutamate, voltage-gated sodium channel blocker (Glu-CB)
- Anticonvulsant, mood stabilizer, voltage-sensitive sodium channel antagonist

Commonly Prescribed for

(bold for FDA approved)

- **Maintenance treatment of bipolar I disorder**
- **Partial seizures (adjunctive; adults and children ages 2 and older)**
- Generalized seizures of Lennox-Gastaut syndrome (adjunctive; adults and children ages 2 and older)
- Primary generalized tonic-clonic seizures (adjunctive; adults and children ages 2 and older)
- Conversion to monotherapy in adults (16 and older) with partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate
- Bipolar depression
- Bipolar mania (adjunctive and second-line)
- Psychosis, schizophrenia (adjunctive)
- Neuropathic pain/chronic pain
- Major depressive disorder (adjunctive)
- Other seizure types and as initial monotherapy for epilepsy



How the Drug Works

- Acts as a use-dependent blocker of voltage-sensitive sodium channels
- Interacts with the open channel conformation of voltage-sensitive sodium channels
- Interacts at a specific site of the alpha pore-forming subunit of voltage-sensitive sodium channels
- Inhibits release of glutamate and aspartate

How Long Until It Works

- May take several weeks to improve bipolar depression

- May take several weeks to months to optimize an effect on mood stabilization
- Can reduce seizures by 2 weeks, but may take several weeks to months to reduce seizures

If It Works

- The goal of treatment is complete remission of symptoms (e.g., seizures, depression, pain)
- Continue treatment until all symptoms are gone or until improvement is stable and then continue treating indefinitely as long as improvement persists
- Continue treatment indefinitely to avoid recurrence of mania, depression, and/or seizures
- Treatment of chronic neuropathic pain may reduce but does not eliminate pain symptoms and is not a cure since pain usually recurs after medicine stopped

If It Doesn't Work (for bipolar disorder)

- Many patients have only a partial response where some symptoms are improved but others persist or continue to wax and wane without stabilization of mood
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent, or adding an appropriate augmenting agent
- Consider adding psychotherapy
- Consider biofeedback or hypnosis for pain
- Consider the presence of noncompliance and counsel patient
- Switch to another mood stabilizer with fewer side effects
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)

Best Augmenting Combos for Partial Response or Treatment Resistance (for bipolar disorder)

- Lithium
- Atypical antipsychotics (especially risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole)
- Valproate (with caution and at half dose of lamotrigine in the presence of valproate,

because valproate can double lamotrigine levels)

* Antidepressants (with caution because antidepressants can destabilize mood in some patients, including induction of rapid cycling or suicidal ideation; in particular consider bupropion; also SSRIs, SNRIs, others; generally avoid TCAs, MAOIs)

Tests

- None required
- The value of monitoring plasma concentrations of lamotrigine has not been established
- Because lamotrigine binds to melanin-containing tissues, ophthalmological checks may be considered

SIDE EFFECTS

How Drug Causes Side Effects

- CNS side effects theoretically due to excessive actions at voltage-sensitive sodium channels
- Rash hypothetically an allergic reaction

Notable Side Effects

- * Benign rash (approximately 10%)
- Dose dependent: blurred or double vision, dizziness, ataxia
 - Sedation, headache, tremor, insomnia, poor coordination, fatigue
 - Nausea (dose-dependent), vomiting, dyspepsia, rhinitis
 - Additional effects in pediatric patients with epilepsy: infection, pharyngitis, asthenia



Life-Threatening or Dangerous Side Effects

- * Rare serious rash (risk may be greater in pediatric patients but still rare)
- Rare multi-organ failure associated with Stevens-Johnson syndrome, toxic epidermal necrolysis, or drug hypersensitivity syndrome
 - Rare blood dyscrasias
 - Rare aseptic meningitis
 - Rare sudden unexplained deaths have occurred in epilepsy (unknown if related to lamotrigine use)
 - Withdrawal seizures upon abrupt withdrawal
 - Rare activation of suicidal ideation and behavior (suicidality)

Weight Gain



- Reported but not expected

Sedation



- Reported but not expected
- Dose-related
- Can wear off with time

What to Do About Side Effects

- Wait
- Take at night to reduce daytime sedation
- Divide dosing to twice daily
- * If patient develops signs of a rash with benign characteristics (i.e., a rash that peaks within days, settles in 10–14 days, is spotty, nonconfluent, nontender, has no systemic features, and laboratory tests are normal):
 - Reduce lamotrigine dose or stop dosage increase
 - Warn patient to stop drug and contact physician if rash worsens or new symptoms emerge
 - Prescribe antihistamine and/or topical corticosteroid for pruritis
 - Monitor patient closely
- * If patient develops signs of a rash with serious characteristics (i.e., a rash that is confluent and widespread, or purpuric or tender; with any prominent involvement of neck or upper trunk; any involvement of eyes, lips, mouth, etc.; any associated fever, malaise, pharyngitis, anorexia, or lymphadenopathy; abnormal laboratory tests for complete blood count, liver function, urea, creatinine):
 - Stop lamotrigine (and valproate if administered)
 - Monitor and investigate organ involvement (hepatic, renal, hematologic)
 - Patient may require hospitalization
 - Monitor patient very closely

Best Augmenting Agents for Side Effects

- Antihistamines and/or topical corticosteroid for rash, pruritis
- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- Monotherapy for bipolar disorder: 100–200 mg/day
- Adjunctive treatment for bipolar disorder: 100 mg/day in combination with valproate; 400 mg/day in combination with enzyme-inducing antiepileptic drugs such as carbamazepine, phenobarbital, phenytoin, and primidone
- Monotherapy for seizures in patients over age 12: 300–500 mg/day in 2 doses
- Adjunctive treatment for seizures in patients over age 12: 100–400 mg/day for regimens containing valproate; 100–200 mg/day for valproate alone; 300–500 mg/day in 2 doses for regimens not containing valproate
- Patients ages 2–12 with epilepsy are dosed based on body weight and concomitant medications

Dosage Forms

- Tablet 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg
- Chewable tablet 2 mg, 5 mg, 25 mg, 100 mg
- Orally disintegrating tablet 25 mg, 50 mg, 100 mg, 200 mg
- Extended-release tablet 25 mg, 50 mg, 100 mg, 200 mg, 250 mg, 300 mg

How to Dose

* Bipolar disorder (monotherapy, see chart): for the first 2 weeks administer

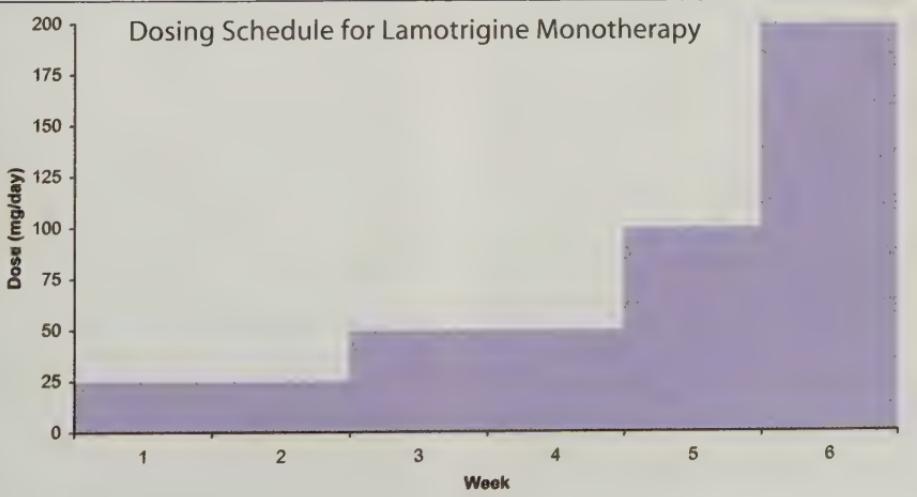
25 mg/day; at week 3 increase to 50 mg/day; at week 5 increase to 100 mg/day; at week 6 increase to 200 mg/day; maximum dose generally 200 mg/day

* Bipolar disorder (adjunct to valproate): for the first 2 weeks administer 25 mg every other day; at week 3 increase to 25 mg/day; at week 5 increase to 50 mg/day; at week 6 increase to 100 mg/day; maximum dose generally 100 mg/day

Bipolar disorder (adjunct to enzyme-inducing antiepileptic drugs): for the first 2 weeks administer 50 mg/day; at week 3 increase to 100 mg/day in divided doses; starting at week 5 increase by 100 mg/day each week; maximum dose generally 400 mg/day in divided doses

When lamotrigine is added to epilepsy treatment that includes valproate (ages 12 and older): for the first 2 weeks administer 25 mg every other day; at week 3 increase to 25 mg/day; every 1–2 weeks can increase by 25–50 mg/day; usual maintenance dose 100–400 mg/day in 1–2 doses or 100–200 mg/day if lamotrigine is added to valproate alone

When lamotrigine is added to epilepsy treatment that includes carbamazepine, phenytoin, phenobarbital, or primidone (without valproate) (ages 12 and older): for the first 2 weeks administer 50 mg/day; at week 3 increase to 100 mg/day in 2 doses; every 1–2 weeks can increase by 100 mg/day; usual maintenance dose 300–500 mg/day in 2 doses



- When converting from a single enzyme-inducing antiepileptic drug to lamotrigine monotherapy for epilepsy: titrate as described above to 500 mg/day in 2 doses while maintaining dose of previous medication; decrease first drug in 20% decrements each week over the next 4 weeks
- When converting from valproate to lamotrigine monotherapy for epilepsy: titrate as described above to 200 mg/day while maintaining dose of valproate, then gradually increase lamotrigine up to 500 mg/day while gradually discontinuing valproate
- Seizures (under age 12): see Children and Adolescents



Dosing Tips

- Very slow dose titration may reduce the incidence of skin rash
- Therefore, dose should not be titrated faster than recommended because of possible risk of increased side effects, including rash
- If patient stops taking lamotrigine for 5 days or more it may be necessary to restart the drug with the initial dose titration, as rashes have been reported on reexposure
- Advise patient to avoid new medications, foods, or products during the first 3 months of lamotrigine treatment in order to decrease the risk of unrelated rash; patient should also not start lamotrigine within 2 weeks of a viral infection, rash, or vaccination

• If lamotrigine is added to patients taking valproate, remember that valproate inhibits lamotrigine metabolism and therefore titration rate and ultimate dose of lamotrigine should be reduced by 50% to reduce the risk of rash

• Thus, if concomitant valproate is discontinued after lamotrigine dose is stabilized, then the lamotrigine dose should be cautiously doubled over at least 2 weeks in equal increments each week following discontinuation of valproate

• Also, if concomitant enzyme-inducing antiepileptic drugs such as carbamazepine, phenobarbital, phenytoin, and primidone are discontinued after lamotrigine dose is stabilized, then the lamotrigine dose

should be maintained for 1 week following discontinuation of the other drug and then reduced by half over 2 weeks in equal decrements each week

- Since oral contraceptives and pregnancy can decrease lamotrigine levels, adjustments to the maintenance dose of lamotrigine are recommended in women taking, starting, or stopping oral contraceptives, becoming pregnant, or after delivery
- Chewable dispersible tablets should only be administered as whole tablets; dose should be rounded down to the nearest whole tablet
- Chewable dispersible tablets can be dispersed by adding the tablet to liquid (enough to cover the drug); after approximately 1 minute the solution should be stirred and then consumed immediately in its entirety
- Orally disintegrating tablet should be placed onto the tongue and moved around in the mouth; the tablet will disintegrate rapidly and can be swallowed with or without food or water
- Do not break or chew extended-release tablets, as this could alter controlled-release properties

Overdose

- Some fatalities have occurred; ataxia, nystagmus, seizures, coma, intraventricular conduction delay

Long-Term Use

- Safe

Habit Forming

- No

How to Stop

- Taper over at least 2 weeks
- Rapid discontinuation can increase the risk of relapse in bipolar disorder
- Patients with epilepsy may seize upon withdrawal, especially if withdrawal is abrupt
- Discontinuation symptoms uncommon

Pharmacokinetics

- Elimination half-life in healthy volunteers approximately 33 hours after a single dose of lamotrigine
- Elimination half-life in patients receiving concomitant valproate treatment

- approximately 59 hours after a single dose of lamotrigine
- Elimination half-life in patients receiving concomitant enzyme-inducing antiepileptic drugs (such as carbamazepine, phenobarbital, phenytoin, and primidone) approximately 14 hours after a single dose of lamotrigine
- Metabolized in the liver through glucuronidation but not through the CYP450 enzyme system
- Inactive metabolite
- Renally excreted
- Lamotrigine inhibits dihydrofolate reductase and may therefore reduce folate concentrations
- Rapidly and completely absorbed; bioavailability not affected by food



Drug Interactions

- Valproate increases plasma concentrations and half-life of lamotrigine, requiring lower doses of lamotrigine (half or less)
- Use of lamotrigine with valproate may be associated with an increased incidence of rash
- Enzyme-inducing antiepileptic drugs (e.g., carbamazepine, phenobarbital, phenytoin, primidone) may increase the clearance of lamotrigine and lower its plasma levels
- Oral contraceptives may decrease plasma levels of lamotrigine
- No likely pharmacokinetic interactions of lamotrigine with lithium, oxcarbazepine, atypical antipsychotics, or antidepressants
- False-positive urine immunoassay screening tests for phencyclidine (PCP) have been reported in patients taking lamotrigine due to a lack of specificity of the screening tests



Other Warnings/ Precautions

- Life-threatening rashes have developed in association with lamotrigine use; lamotrigine should generally be discontinued at the first sign of serious rash
- Risk of rash may be increased with higher doses, faster dose escalation, concomitant use of valproate, or in children under age 12

- Patient should be instructed to report any symptoms of hypersensitivity immediately (fever; flu-like symptoms; rash; blisters on skin or in eyes, mouth, ears, nose, or genital areas; swelling of eyelids, conjunctivitis, lymphadenopathy)
- Aseptic meningitis has been reported rarely in association with lamotrigine use
- Patients should be advised to report any symptoms of aseptic meningitis immediately; these include headache, chills, fever, vomiting and nausea, a stiff neck, and sensitivity to light
- Depressive effects may be increased by other CNS depressants (alcohol, MAOIs, other anticonvulsants, etc.)
- A small number of people may experience a worsening of seizures
- May cause photosensitivity
- Lamotrigine binds to tissue that contains melanin, so for long-term treatment ophthalmological checks may be considered
- Warn patients and their caregivers about the possibility of activation of suicidal ideation and advise them to report such side effects immediately

Do Not Use

- If there is a proven allergy to lamotrigine

SPECIAL POPULATIONS

Renal Impairment

- Lamotrigine is renally excreted, so the maintenance dose may need to be lowered
- Can be removed by hemodialysis; patients receiving hemodialysis may require supplemental doses of lamotrigine

Hepatic Impairment

- Dose adjustment not necessary in mild impairment
- Initial, escalation, and maintenance doses should be reduced by 25% in patients with moderate and severe liver impairment without ascites and 50% in patients with severe liver impairment with ascites

Cardiac Impairment

- Clinical experience is limited
- Drug should be used with caution

Elderly

- Some patients may tolerate lower doses better
- Elderly patients may be more susceptible to adverse effects



Children and Adolescents

- Ages 2 and older: approved as add-on for Lennox-Gastaut syndrome
- Ages 2 and older: approved as add-on for partial seizures
- No other use of lamotrigine is approved for patients under 16 years of age
- Risk of rash is increased in pediatric patients, especially in children under 12 and in children taking valproate
- When lamotrigine is added to treatment that includes valproate (ages 2–12): for the first 2 weeks administer 0.15 mg/kg per day in 1–2 doses rounded down to the nearest whole tablet; at week 3 increase to 0.3 mg/kg per day in 1–2 doses rounded down to the nearest whole tablet; every 1–2 weeks can increase by 0.3 mg/kg per day rounded down to the nearest whole tablet; usual maintenance dose 1–5 mg/kg per day in 1–2 doses (maximum generally 200 mg/day) or 1–3 mg/kg per day in 1–2 doses if lamotrigine is added to valproate alone
- When lamotrigine is added to treatment with carbamazepine, phenytoin, phenobarbital, or primidone (without valproate) (ages 2–12): for the first 2 weeks administer 0.6 mg/kg per day in 2 doses rounded down to the nearest whole tablet; at week 3 increase to 1.2 mg/kg per day in 2 doses rounded down to the nearest whole tablet; every 1–2 weeks can increase by 1.2 mg/kg per day rounded down to the nearest whole tablet; usual maintenance dose 5–15 mg/kg per day in 2 doses (maximum dose generally 400 mg per day)
- Clearance of lamotrigine may be influenced by weight, such that patients weighing less than 30 kg may require an increase of up to 50% for maintenance doses



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information

in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001

- Controlled studies have not been conducted in pregnant women
- Use in women of childbearing potential requires weighing potential benefits to the mother against the risks to the fetus
- Pregnancy registry data show increased risk of isolated cleft palate or cleft lip deformity with first trimester exposure
- Risk of rash is increased in pediatric patients, especially in children under 12 and in children taking valproate
- If treatment with lamotrigine is continued, plasma concentrations of lamotrigine may be reduced during pregnancy, possibly requiring increased doses with dose reduction following delivery
- Pregnancy exposure registry for lamotrigine: (800) 336–2176
- Taper drug if discontinuing
- Seizures, even mild seizures, may cause harm to the embryo/fetus
- Recurrent bipolar illness during pregnancy can be quite disruptive
- For bipolar patients, lamotrigine should generally be discontinued before anticipated pregnancies
- For bipolar patients in whom treatment is discontinued, given the risk of relapse in the postpartum period, lamotrigine should generally be restarted immediately after delivery
- Atypical antipsychotics may be preferable to lithium or anticonvulsants such as lamotrigine if treatment of bipolar disorder is required during pregnancy, but lamotrigine may be preferable to other anticonvulsants such as valproate if anticonvulsant treatment is required during pregnancy
- Bipolar symptoms may recur or worsen during pregnancy and some form of treatment may be necessary

Breast Feeding

- Some drug is found in mother's breast milk
- Generally recommended either to discontinue drug or bottle feed
- If drug is continued while breast feeding, infant should be monitored for possible adverse effects

- If infant shows signs of irritability or sedation, drug may need to be discontinued
- ✿ Bipolar disorder may recur during the postpartum period, particularly if there is a history of prior postpartum episodes of either depression or psychosis
- ✿ Relapse rates may be lower in women who receive prophylactic treatment for postpartum episodes of bipolar disorder
- Atypical antipsychotics and anticonvulsants such as valproate may be preferable to lithium or lamotrigine during the postpartum period when breast feeding

convincing evidence of efficacy in bipolar disorder (e.g., gabapentin or topiramate)

- ✿ Low levels of use may be based upon exaggerated fears of skin rashes or lack of knowledge about how to manage skin rashes if they occur
- ✿ May actually be one of the best tolerated mood stabilizers with little weight gain or sedation
- Actual risk of serious skin rash may be comparable to agents erroneously considered "safer" including carbamazepine, phenytoin, phenobarbital, and zonisamide
- Rashes are common even in placebo-treated patients in clinical trials of bipolar patients (5–10%) due to non-drug related causes including eczema, irritant, and allergic contact dermatitis, such as poison ivy and insect bite reactions

- ✿ To manage rashes in bipolar patients receiving lamotrigine, realize that rashes that occur within the first 5 days or after 8–12 weeks of treatment are rarely drug-related, and learn the clinical distinctions between a benign rash and a serious rash (see What to Do About Side Effects section)
- Rash, including serious rash, appears riskiest in younger children, in those who are receiving concomitant valproate, and/or in those receiving rapid lamotrigine titration and/or high dosing
- Risk of serious rash is less than 1% and has been declining since slower titration, lower dosing, adjustments to use of concomitant valproate administration, and limitations on use in children under 12 have been implemented
- Incidence of serious rash is very low (approaching zero) in recent studies of bipolar patients
- Benign rashes related to lamotrigine may affect up to 10% of patients and resolve rapidly with drug discontinuation
- ✿ Given the limited treatment options for bipolar depression, patients with benign rashes can even be rechallenged with lamotrigine 5–12 mg/day with very slow titration after risk/benefit analysis if they are informed, reliable, closely monitored, and warned to stop lamotrigine and contact their physician if signs of hypersensitivity occur

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Depressive stages of bipolar disorder (bipolar depression)
- To prevent recurrences of both depression and mania in bipolar disorder

Potential Disadvantages

- May not be as effective in the manic stage of bipolar disorder

Primary Target Symptoms

- Incidence of seizures
- Unstable mood, especially depression, in bipolar disorder
- Pain



Pearls

- ✿ Lamotrigine is a first-line treatment option that may be best for patients with bipolar depression
- ✿ Seems to be more effective in treating depressive episodes than manic episodes in bipolar disorder (treats from below better than it treats from above)
- ✿ Seems to be effective in preventing both manic relapses as well as depressive relapses (stabilizes both from above and from below) although it may be even better for preventing depressive relapses than for preventing manic relapses
- ✿ Despite convincing evidence of efficacy in bipolar disorder, is often used less frequently than anticonvulsants without

- Only a third of bipolar patients experience adequate relief with a monotherapy, so most patients need multiple medications for best control
- Lamotrigine is useful in combination with atypical antipsychotics and/or lithium for acute mania
- Usefulness for bipolar disorder in combination with anticonvulsants other than valproate is not well demonstrated; such combinations can be expensive and are possibly ineffective or even irrational
- May be useful as an adjunct to atypical antipsychotics for rapid onset of action in schizophrenia
- May be useful as an adjunct to antidepressants in major depressive disorder
- Early studies suggest possible utility for patients with neuropathic pain such as diabetic peripheral neuropathy, HIV-associated neuropathy, and other pain conditions including migraine



Suggested Reading

Calabrese JR, Bowden CL, Sachs GS, et al. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. *J Clin Psych* 1999;60:79–88.

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Cunningham M, Tennis P, and the International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Lamotrigine and the risk of malformations in pregnancy. *Neurology* 2005;64:955–60.

Goodwin GM, Bowden CL, Calabrese JR, et al. A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance treatment in bipolar I disorder. *J Clin Psychiatry* 2004;65:432–41.

Green B. Lamotrigine in mood disorders. *Curr Med Res Opin* 2003;19:272–7.

THERAPEUTICS

Brands • Vyvanse*see index for additional brand names***Generic?** No **Class**

- Neuroscience-based Nomenclature: dopamine and norepinephrine reuptake inhibitor and releaser (DN-RIRe)
- Stimulant

Commonly Prescribed for*(bold for FDA approved)*

- **Attention deficit hyperactivity disorder (ADHD) (ages 6 and older)**
- **Binge eating disorder**
- Narcolepsy
- Treatment-resistant depression

**How the Drug Works**

＊ Lisdexamfetamine is a prodrug of dextroamphetamine and is thus not active until after it has been absorbed by the intestinal tract and converted to dextroamphetamine (active component) and l-lysine

- ＊ Once converted to dextroamphetamine, it increases norepinephrine and especially dopamine actions by blocking their reuptake and facilitating their release
- Enhancement of dopamine and norepinephrine in certain brain regions (e.g., dorsolateral prefrontal cortex) may improve attention, concentration, executive dysfunction, and wakefulness
 - Enhancement of dopamine actions in other brain regions (e.g., basal ganglia) may improve hyperactivity
 - Enhancement of dopamine and norepinephrine in yet other brain regions (e.g., medial prefrontal cortex, hypothalamus) may improve depression, fatigue, and sleepiness

How Long Until It Works

- Some immediate effects can be seen with first dosing
- Can take several weeks to attain maximum therapeutic benefit

If It Works (for ADHD)

- The goal of treatment of ADHD is reduction of symptoms of inattentiveness, motor hyperactivity, and/or impulsiveness that disrupt social, school, and/or occupational functioning
- Continue treatment until all symptoms are under control or improvement is stable and then continue treatment indefinitely as long as improvement persists
- Reevaluate the need for treatment periodically
- Treatment for ADHD begun in childhood may need to be continued into adolescence and adulthood if continued benefit is documented

If It Doesn't Work (for ADHD)

- Consider adjusting dose or switching to another formulation of d-amphetamine or to another agent
 - Consider behavioral therapy
 - Consider the presence of noncompliance and counsel patients and parents
 - Consider evaluation for another diagnosis or for a comorbid condition (e.g., bipolar disorder, substance abuse, medical illness, etc.)
- ＊ Some ADHD patients and some depressed patients may experience lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require either augmenting with a mood stabilizer or switching to a mood stabilizer

**Best Augmenting Combos for Partial Response or Treatment Resistance**

- ＊ Best to attempt other monotherapies prior to augmenting
- For the expert, can combine with modafinil or atomoxetine for ADHD
 - For the expert, can occasionally combine with atypical antipsychotics in highly treatment-resistant cases of bipolar disorder or ADHD
 - For the expert, can combine with antidepressants to boost antidepressant efficacy in highly treatment-resistant cases of depression while carefully monitoring patient

Tests

- Before treatment, assess for presence of cardiac disease (history, family history, physical exam)

- Blood pressure should be monitored regularly
- In children, monitor weight and height

SIDE EFFECTS

How Drug Causes Side Effects

- Increases in norepinephrine especially peripherally can cause autonomic side effects, including tremor, tachycardia, hypertension, and cardiac arrhythmias
- Increases in norepinephrine and dopamine centrally can cause CNS side effects such as insomnia, agitation, psychosis, and substance abuse

Notable Side Effects

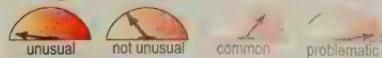
- Insomnia, headache, exacerbation of tics, nervousness, irritability, overstimulation, tremor, dizziness
- Anorexia, nausea, dry mouth, constipation, diarrhea, weight loss
- Can temporarily slow normal growth in children (controversial)
- Sexual dysfunction long-term (impotence, libido changes), but can also improve sexual dysfunction short-term



Life-Threatening or Dangerous Side Effects

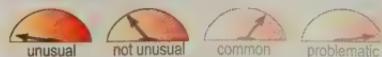
- Psychotic episodes
- Seizures
- Palpitations, tachycardia, hypertension
- Rare activation of hypomania, mania, or suicidal ideation (controversial)
- Cardiovascular adverse effects, sudden death in patients with preexisting cardiac structural abnormalities

Weight Gain



- Reported but not expected
- Some patients may experience weight loss

Sedation



- Reported but not expected
- Activation much more common than sedation

What to Do About Side Effects

- Wait
- Adjust dose
- Switch to another long-acting stimulant
- Switch to another agent
- For insomnia, avoid dosing in afternoon/evening

Best Augmenting Agents for Side Effects

- Beta blockers for peripheral autonomic side effects
- Dose reduction or switching to another agent may be more effective since most side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- ADHD: 30–70 mg/day
- Binge eating disorder: 50–70 mg/day

Dosage Forms

- Capsule 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg

How to Dose

- Initial 30 mg/day in the morning; can increase by 10–20 mg each week; maximum dose generally 70 mg/day
- Binge eating disorder: initial 30 mg/day in the morning; can increase by 20 mg each week; maximum dose generally 70 mg/day



Dosing Tips

- 10–12 hour duration of clinical action
- Capsules can either be taken whole or they can be opened and the contents dissolved in water
- When taken in water, the entire solution should be consumed immediately
- Dose of a single capsule should not be divided
- Once daily dosing can be an important practical element in stimulant utilization, eliminating the hassle and pragmatic difficulties of lunchtime dosing at school, including storage problems, potential diversion, and the need for a medical professional to supervise dosing away from home

- Avoid dosing after the morning because of the risk of insomnia
- May be possible to dose only during the school week for some ADHD patients
- May be able to give drug holidays for patients with ADHD over the summer in order to reassess therapeutic utility and effects on growth suppression as well as to assess any other side effects and the need to reinstitute stimulant treatment for the next school term
- Can be taken with or without food

Overdose

- Rarely fatal; panic, hyperreflexia, rhabdomyolysis, rapid respiration, confusion, coma, hallucination, convulsion, arrhythmia, change in blood pressure, circulatory collapse

Long-Term Use

- Can be used long-term for ADHD when ongoing monitoring documents continued efficacy
- Dependence and/or abuse may develop
- Tolerance to therapeutic effects may develop in some patients
- Long-term stimulant use may be associated with growth suppression in children (controversial)
- Periodic monitoring of weight, blood pressure, CBC, platelet counts, and liver function may be prudent

Habit Forming

- Schedule II drug
- Patients may develop tolerance, psychological dependence
- Theoretically less abuse potential than other stimulants when taken as directed because it is inactive until it reaches the gut and thus has delayed time to onset as well as long duration of action

How to Stop

- Taper to avoid withdrawal effects
- Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder and may require follow-up and reinstitution of treatment
- Careful supervision is required during withdrawal from abuse use since severe depression may occur

Pharmacokinetics

- 1 hour to maximum concentration of lisdexamfetamine, 3.5 hours to maximum concentration of dextroamphetamine
- Duration of clinical action 10–12 hours



Drug Interactions

- May affect blood pressure and should be used cautiously with agents used to control blood pressure
- Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid, ascorbic acid, fruit juices, etc.) and urinary acidifying agents (ammonium chloride, sodium phosphate, etc.) lower amphetamine plasma levels, so such agents can be useful to administer after an overdose but may also lower therapeutic efficacy of amphetamines
- Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) and urinary alkalinizing agents (acetazolamide, some thiazides) increase amphetamine plasma levels and potentiate amphetamine's actions
- Desipramine and protryptiline can cause striking and sustained increases in brain concentrations of d-amphetamine and may also add to d-amphetamine's cardiovascular effects
- Theoretically, other agents with norepinephrine reuptake blocking properties, such as venlafaxine, duloxetine, atomoxetine, milnacipran, and reboxetine, could also add to amphetamine's CNS and cardiovascular effects
- Amphetamines may counteract the sedative effects of antihistamines
- Haloperidol, chlorpromazine, and lithium may inhibit stimulatory effects of amphetamine
- Theoretically, atypical antipsychotics should also inhibit stimulatory effects of amphetamines
- Theoretically, amphetamines could inhibit the antipsychotic actions of antipsychotics
- Theoretically, amphetamines could inhibit the mood-stabilizing actions of atypical antipsychotics in some patients
- Combinations of amphetamines with mood stabilizers (lithium, anticonvulsants, atypical antipsychotics) is generally something for experts only, when

monitoring patients closely and when other options fail

- Absorption of phenobarbital, phenytoin, and ethosuximide is delayed by amphetamines
- Amphetamines inhibit adrenergic blockers and enhance adrenergic effects of norepinephrine
- Amphetamines may antagonize hypotensive effects of Veratrum alkaloids and other antihypertensives
- Amphetamines increase the analgesic effects of meperidine
- Amphetamines contribute to excessive CNS stimulation if used with large doses of propoxyphene
- Amphetamines can raise plasma corticosteroid levels
- MAOIs slow absorption of amphetamines and thus potentiate their actions, which can cause headache, hypertension, and rarely hypertensive crisis and malignant hyperthermia, sometimes with fatal results
- Use with MAOIs, including within 14 days of MAOI use, is not advised, but this can sometimes be considered by experts who monitor depressed patients closely when other treatment options for depression fail



Other Warnings/ Precautions

- Use with caution in patients with any degree of hypertension, hyperthyroidism, or history of drug abuse
- Children who are not growing or gaining weight should stop treatment, at least temporarily
- May worsen motor and phonic tics
- May worsen symptoms of thought disorder and behavior disturbance in psychotic patients
- Stimulants have a high potential for abuse and must be used with caution in anyone with a current or past history of substance abuse or alcoholism or in emotionally unstable patients
- Administration of stimulants for prolonged periods of time should be avoided whenever possible or done only with close monitoring, as it may lead to marked tolerance and drug dependence, including psychological dependence with varying degrees of abnormal behavior

- Particular attention should be paid to the possibility of subjects obtaining stimulants for nontherapeutic use or distribution to others and the drugs should in general be prescribed sparingly with documentation of appropriate use
- Usual dosing has been associated with sudden death in children with structural cardiac abnormalities
- Not an appropriate first-line treatment for depression or for normal fatigue
- May lower the seizure threshold
- Emergence or worsening of activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of a mood stabilizer and/or discontinuation of lisdexamfetamine

Do Not Use

- If patient has extreme anxiety or agitation
- If patient has motor tics or Tourette's syndrome or if there is a family history of Tourette's, unless administered by an expert in cases when the potential benefits for ADHD outweigh the risks of worsening tics
- Should generally not be administered with an MAOI, including within 14 days of MAOI use, except in heroic circumstances and by an expert
- If patient has arteriosclerosis, cardiovascular disease, or severe hypertension
- If patient has glaucoma
- If patient has structural cardiac abnormalities
- If patient has hyperthyroidism
- If there is a proven allergy to any sympathomimetic agent

SPECIAL POPULATIONS

Renal Impairment

- Severe impairment: maximum dose 50 mg/day
- End-stage renal disease: maximum dose 30 mg/day

Hepatic Impairment

- Use with caution

Cardiac Impairment

- Use with caution, particularly in patients with recent myocardial infarction or other conditions that could be negatively affected by increased blood pressure
- Do not use in patients with structural cardiac abnormalities, cardiac myopathy, serious heart arrhythmia, or coronary artery disease

Elderly

- Some patients may tolerate lower doses better



Children and Adolescents

- Safety and efficacy not established in children under age 6
- Use in young children should be reserved for the expert
- d-amphetamine may worsen symptoms of behavioral disturbance and thought disorder in psychotic children
- d-amphetamine has acute effects on growth hormone; long-term effects are unknown but weight and height should be monitored during long-term treatment
- Sudden death in children and adolescents with serious heart problems has been reported
- American Heart Association recommends EKG prior to initiating stimulant treatment in children, although not all experts agree



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- There is a greater risk of premature birth and low birth weight in infants whose mothers take d-amphetamine during pregnancy

- Infants whose mothers take d-amphetamine during pregnancy may experience withdrawal symptoms
- In animal studies, d-amphetamine caused delayed skeletal ossification and decreased post-weaning weight gain in rats; no major malformations occurred in rat or rabbit studies
- Use in women of childbearing potential requires weighing potential benefits to the mother against potential risks to the fetus
- For ADHD patients, lisdexamfetamine should generally be discontinued before anticipated pregnancies

Breast Feeding

- Some drug is found in mother's breast milk
- Recommended either to discontinue drug or bottle feed
- If infant shows signs of irritability, drug may need to be discontinued

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Only approved treatment for binge eating disorder
- Although restricted as a Schedule II controlled substance like other stimulants, as a prodrug lisdexamfetamine may have less propensity for abuse, intoxication, or dependence than other stimulants
- May be particularly useful in adult patients without prior diagnosis and treatment of ADHD as a child to prevent abuse and diversion since lisdexamfetamine may be less abusable than other stimulants

Potential Disadvantages

- Patients with current or past substance abuse
- Patients with current or past bipolar disorder or psychosis

Primary Target Symptoms

- Concentration, attention span
- Motor hyperactivity
- Impulsiveness
- Binge eating
- Physical and mental fatigue
- Daytime sleepiness
- Depression



Pearls

- First medication approved for the treatment of binge eating disorder
- Theoretically, efficacy in binge eating disorder is due to controlled-release of a stimulant enhancing tonic over phasic dopamine neuronal firing
- Theoretically, binge eating in binge eating disorder could be due to a shift from reward-related eating to habit, and from impulsivity to compulsivity due to a shift of control of dopamine from dorsal to ventral striatum, which can be reversed by lisdexamfetamine
- May be useful for treatment of depressive symptoms in medically ill elderly patients
- May be useful for treatment of post-stroke depression
- A classical augmentation strategy for treatment-refractory depression
- Specifically, may be useful for treatment of cognitive dysfunction and fatigue as residual symptoms of major depressive disorder unresponsive to multiple prior treatments
- May also be useful for the treatment of cognitive impairment, depressive

symptoms, and severe fatigue in patients with HIV infection and in cancer patients

- Can be used to potentiate opioid analgesia and reduce sedation, particularly in end-of-life management
- Some patients respond to or tolerate lisdexamfetamine better than methylphenidate or amphetamine and vice versa
- *** Despite warnings, can be a useful adjunct to MAOIs for heroic treatment of highly refractory mood disorders when monitored with vigilance**
- *** Can reverse sexual dysfunction caused by psychiatric illness and by some drugs such as SSRIs, including decreased libido, erectile dysfunction, delayed ejaculation, and anorgasmia**
- Atypical antipsychotics may be useful in treating stimulant or psychotic consequences of overdose
- Half-life and duration of clinical action tend to be shorter in younger children
- Drug abuse may actually be lower in ADHD adolescents treated with stimulants than in ADHD adolescents who are not treated



Suggested Reading

Biederman J, Boellner SW, Childress A, et al. Lisdexamfetamine dimesylate and mixed amphetamine salts extended-release in children with ADHD: a double-blind, placebo-controlled, crossover analog classroom study. *Biol Psychiatry* 2007;62(9):970-6.

Biederman J, Krishnan S, Zhang Y, McGough JJ, Findling RL. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced dose, parallel-group study. *Clin Ther* 2007;29(3):450-63.

THERAPEUTICS

Brands

- Eskalith
- Eskalith CR
- Lithobid slow-release tablets
- Lithostat tablets
- Lithium carbonate tablets
- Lithium citrate syrup

see index for additional brand names

Generic? Yes



Class

- Neuroscience-based Nomenclature: lithium enzyme interactions (Li-Eint)
- Mood stabilizer

Commonly Prescribed for

(bold for FDA approved)

- **Manic episodes of manic-depressive illness**
- **Maintenance treatment for manic-depressive patients with a history of mania**
- Bipolar depression
- Major depressive disorder (adjunctive)
- Vascular headache
- Neutropenia



How the Drug Works

- Unknown and complex
- Alters sodium transport across cell membranes in nerve and muscle cells
- Alters metabolism of neurotransmitters including catecholamines and serotonin
- May alter intracellular signaling through actions on second messenger systems
- Specifically, inhibits inositol monophosphatase, possibly affecting neurotransmission via phosphatidyl inositol second messenger system
- Also reduces protein kinase C activity, possibly affecting genomic expression associated with neurotransmission
- Increases cytoprotective proteins, activates signaling cascade utilized by endogenous growth factors, and increases gray matter content, possibly by activating neurogenesis and enhancing trophic actions that maintain synapses

How Long Until It Works

- 1–3 weeks

If It Works

- The goal of treatment is complete remission of symptoms (i.e., mania and/or depression)
- Continue treatment until all symptoms are gone or until improvement is stable and then continue treating indefinitely as long as improvement persists
- Continue treatment indefinitely to avoid recurrence of mania or depression

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist or continue to wax and wane without stabilization of mood
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider checking plasma drug level, increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider adding psychotherapy
- Consider the presence of noncompliance and counsel patient
- Switch to another mood stabilizer with fewer side effects
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)



Best Augmenting Combos for Partial Response or Treatment Resistance

- Valproate
- Atypical antipsychotics (especially risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole)
- Lamotrigine
- Antidepressants (with caution because antidepressants can destabilize mood in some patients, including induction of rapid cycling or suicidal ideation; in particular consider bupropion; also SSRIs, SNRIs, others; generally avoid TCAs, MAOIs)

Tests

- Before initiating treatment, kidney function tests (including creatinine and urine specific gravity) and thyroid function tests; electrocardiogram for patients over 50
- Repeat kidney function tests 1–2 times/year

- ✿ Frequent tests to monitor trough lithium plasma levels (about 12 hours after last dose; should generally be between 1.0 and 1.5 mEq/L for acute treatment, 0.6 and 1.2 mEq/L for chronic treatment)
- ✿ Initial monitoring: every 1–2 weeks until desired serum concentration is achieved, then every 2–3 months for the first 6 months
- ✿ Stable monitoring: every 6–12 months
- ✿ One-off monitoring after dose change, other medication change, illness change (not before 1 week)
- ✿ Since lithium is frequently associated with weight gain, before starting treatment, weigh all patients and determine if the patient is already overweight (BMI 25.0–29.9) or obese (BMI ≥ 30)
- Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–125 mg/dL), diabetes (fasting plasma glucose > 126 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management
- ✿ Monitor weight and BMI during treatment
- ✿ While giving a drug to a patient who has gained $> 5\%$ of initial weight, consider evaluating for the presence of pre-diabetes, diabetes, or dyslipidemia, or consider switching to a different agent

SIDE EFFECTS

How Drug Causes Side Effects

- Unknown and complex
- CNS side effects theoretically due to excessive actions at the same or similar sites that mediate its therapeutic actions
- Some renal side effects theoretically due to lithium's actions on ion transport

Notable Side Effects

- ✿ Ataxia, dysarthria, delirium, tremor, memory problems
- ✿ Polyuria, polydipsia (nephrogenic diabetes insipidus)

- ✿ Diarrhea, nausea
- ✿ Weight gain
- Euthyroid goiter or hypothyroid goiter, possibly with increased TSH and reduced thyroxine levels
- Acne, rash, alopecia
- Leukocytosis
- Side effects are typically dose-related



Life-Threatening or Dangerous Side Effects

- Lithium toxicity
- Renal impairment (interstitial nephritis)
- Nephrogenic diabetes insipidus
- Arrhythmia, cardiovascular changes, sick sinus syndrome, bradycardia, hypotension
- T wave flattening and inversion
- Rare pseudotumor cerebri
- Rare seizures

Weight Gain



- Many experience and/or can be significant in amount
- Can become a health problem in some
- May be associated with increased appetite

Sedation



- Many experience and/or can be significant in amount
- May wear off with time

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- ✿ Take entire dose at night as long as efficacy persists all day long with this administration
- ✿ Change to a different lithium preparation (e.g., controlled-release)
- ✿ Reduce dosing from 3 times/day to 2 times/day
- If signs of lithium toxicity occur, discontinue immediately
- For stomach upset, take with food
- For tremor, avoid caffeine
- Switch to another agent

Best Augmenting Agents for Side Effects

- * Propranolol 20–30 mg 2–3 times/day may reduce tremor
- For the expert, cautious addition of a diuretic (e.g., chlorothiazide 50 mg/day) while reducing lithium dose by 50% and monitoring plasma lithium levels may reduce polydipsia and polyuria that does not go away with time alone
- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- Mania: recommended 1.0–1.5 mEq/L
- Depression: recommended 0.6–1.0 mEq/L
- Maintenance: recommended 0.7–1.0 mEq/L
- Liquid: 10 mL three times/day (acute mania); 5 mL 3–4 times/day (long-term)

Dosage Forms

- Tablet 300 mg (slow-release), 450 mg (controlled-release)
- Capsule 150 mg, 300 mg, 600 mg
- Liquid 8 mEq/5 mL

How to Dose

- Start 300 mg 2–3 times/day and adjust dosage upward as indicated by plasma lithium levels



Dosing Tips

- * Sustained-release formulation may reduce gastric irritation, lower peak lithium plasma levels, and diminish peak dose side effects (i.e., side effects occurring 1–2 hours after each dose of standard lithium carbonate may be improved by sustained-release formulation)
- Lithium sulfate and other dosage strengths for lithium are available in Europe
- Check therapeutic blood levels as “trough” levels about 12 hours after the last dose
- After stabilization, some patients may do best with a once daily dose at night
- Responses in acute mania may take 7–14 days even with adequate plasma lithium levels
- * Some patients apparently respond to doses as low as 300 mg twice a day, even with plasma lithium levels below 0.5 mEq/L

- Use the lowest dose of lithium associated with adequate therapeutic response
- Lower doses and lower plasma lithium levels (<0.6 mEq/L) are often adequate and advisable in the elderly

- * Rapid discontinuation increases the risk of relapse and possibly suicide, so lithium may need to be tapered slowly over 3 months if it is to be discontinued after long-term maintenance

Overdose

- Fatalities have occurred; tremor, dysarthria, delirium, coma, seizures, autonomic instability

Long-Term Use

- Indicated for long-term prevention of relapse
- May cause reduced kidney function
- Requires regular therapeutic monitoring of lithium levels as well as of kidney function and thyroid function

Habit Forming

- No

How to Stop

- Taper gradually over 3 months to avoid relapse
- Rapid discontinuation increases the risk of relapse, and possibly suicide
- Discontinuation symptoms uncommon

Pharmacokinetics

- Half life 18–30 hours
- Lower absorption on empty stomach



Drug Interactions

- * Non-steroidal anti-inflammatory agents, including ibuprofen and selective COX-2 inhibitors (cyclooxygenase 2), can increase plasma lithium concentrations; add with caution to patients stabilized on lithium
- * Diuretics, especially thiazides, can increase plasma lithium concentrations; add with caution to patients stabilized on lithium
- Angiotensin-converting enzyme inhibitors can increase plasma lithium concentrations; add with caution to patients stabilized on lithium
- Metronidazole can lead to lithium toxicity through decreased renal clearance

- Acetazolamide, alkalinizing agents, xanthine preparations, and urea may lower lithium plasma concentrations
- Methyldopa, carbamazepine, and phenytoin may interact with lithium to increase its toxicity
- Use lithium cautiously with calcium channel blockers, which may also increase lithium toxicity
- Use of lithium with an SSRI may raise risk of dizziness, confusion, diarrhea, agitation, tremor
- Some patients taking haloperidol and lithium have developed an encephalopathic syndrome similar to neuroleptic malignant syndrome
- Lithium may prolong effects of neuromuscular blocking agents
- No likely pharmacokinetic interactions of lithium with mood-stabilizing anticonvulsants or atypical antipsychotics



Other Warnings/ Precautions

- Toxic levels are near therapeutic levels; signs of toxicity include tremor, ataxia, diarrhea, vomiting, sedation
- Monitor for dehydration; lower dose if patient exhibits signs of infection, excessive sweating, diarrhea
- Closely monitor patients with thyroid disorders
- Lithium may cause unmasking of Brugada syndrome; consultation with a cardiologist is recommended if patients develop unexplained syncope or palpitations after starting lithium

Do Not Use

- If patient has severe kidney disease
- If patient has severe cardiovascular disease
- If patient has Brugada syndrome
- If patient has severe dehydration
- If patient has sodium depletion
- If there is a proven allergy to lithium

SPECIAL POPULATIONS

Renal Impairment

- Not recommended for use in patients with severe impairment
- Some experts recommend no dosing modification for glomerular filtration rate (GFR)>50 mL/min

Hepatic Impairment

- No special indications

Cardiac Impairment

- Not recommended for use in patients with severe impairment
- Lithium can cause reversible T-wave changes, sinus bradycardia, sick sinus syndrome, or heart block

Elderly

- Likely that elderly patients will require lower doses to achieve therapeutic serum levels
- Elderly patients may be more sensitive to adverse effects
- *** Neurotoxicity**, including delirium and other mental status changes, may occur even at therapeutic doses in elderly and organically compromised patients
- Lower doses and lower plasma lithium levels (<0.6 mEq/L) are often adequate and advisable in the elderly



Children and Adolescents

- Safety and efficacy not established in children under age 12
- Use only with caution
- Younger children tend to have more frequent and severe side effects
- Children should be monitored more frequently



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001

- Evidence of increased risk of major birth defects (perhaps 2–3 times the general population), but probably lower than with some other mood stabilizers (e.g., valproate)
- Evidence of increase in cardiac anomalies (especially Ebstein's anomaly) in infants

whose mothers took lithium during pregnancy

- No long-term neurobehavioral effects of late-term neonatal lithium exposure have been observed
- If lithium is continued, monitor serum lithium levels every 4 weeks, then every week beginning at 36 weeks
- Dehydration due to morning sickness may cause rapid increases in lithium levels
- Lithium administration during delivery may be associated with hypotonia in the infant; most recommend withholding lithium for 24–48 hours before delivery
- Monitoring during delivery should include fluid balance
- After delivery, monitor for 48 hours for “floppy baby syndrome”
- Use in women of childbearing potential requires weighing potential benefits to the mother against the risks to the fetus
- Recurrent bipolar illness during pregnancy can be quite disruptive
- Taper drug if discontinuing
- Given the risk of bipolar relapse in the postpartum period, lithium should generally be restarted immediately after delivery
- This may mean no breast feeding, since lithium can be found in breast milk, possibly at full therapeutic levels
- ✿ Atypical antipsychotics may be preferable to lithium or anticonvulsants if treatment of bipolar disorder is required during pregnancy
- Bipolar symptoms may recur or worsen during pregnancy and some form of treatment may be necessary

Breast Feeding

- Some drug is found in mother's breast milk, possibly at full therapeutic levels since lithium is soluble in breast milk
- ✿ Recommended either to discontinue drug or bottle feed
- ✿ Bipolar disorder may recur during the postpartum period, particularly if there is a history of prior postpartum episodes of either depression or psychosis
- ✿ Relapse rates may be lower in women who receive prophylactic treatment for postpartum episodes of bipolar disorder
- Atypical antipsychotics and anticonvulsants such as valproate may be safer than lithium during the postpartum period when breast feeding

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Euphoric mania
- Treatment-resistant depression
- Reduces suicide risk
- Works well in combination with atypical antipsychotics and/or mood-stabilizing anticonvulsants such as valproate

Potential Disadvantages

- Dysphoric mania
- Mixed mania, rapid-cycling mania
- Depressed phase of bipolar disorder
- Patients unable to tolerate weight gain, sedation, gastrointestinal effects, renal effects, and other side effects
- Requires blood monitoring

Primary Target Symptoms

- Unstable mood
- Mania



Pearls

- ✿ Lithium was the original mood stabilizer and is still a first-line treatment option but may be underutilized since it is an older agent and is less promoted for use in bipolar disorder than newer agents
- ✿ May be best for euphoric mania; patients with rapid-cycling and mixed state types of bipolar disorder generally do less well on lithium
- ✿ Seems to be more effective in treating manic episodes than depressive episodes in bipolar disorder (treats from above better than it treats from below)
- ✿ May also be more effective in preventing manic relapses than in preventing depressive episodes (stabilizes from above better than it stabilizes from below)
- ✿ May decrease suicide and suicide attempts not only in bipolar I disorder but also in bipolar II disorder and in unipolar depression
- ✿ Due to its narrow therapeutic index, lithium's toxic side effects occur at doses close to its therapeutic effects
- Close therapeutic monitoring of plasma drug levels is required during lithium treatment; lithium is the first psychiatric drug that required blood level monitoring
- Probably less effective than atypical antipsychotics for severe, excited,

disturbed, hyperactive, or psychotic patients with mania

- Due to delayed onset of action, lithium monotherapy may not be the first choice in acute mania, but rather may be used as an adjunct to atypical antipsychotics, benzodiazepines, and/or valproate loading
- After acute symptoms of mania are controlled, some patients can be maintained on lithium monotherapy
- However, only a third of bipolar patients experience adequate relief with a monotherapy, so most patients need multiple medications for best control
- Lithium is not a convincing augmentation agent to atypical antipsychotics for the treatment of schizophrenia
- Lithium is one of the most useful adjunctive agents to augment antidepressants for treatment-resistant unipolar depression
- Lithium may be useful for a number of patients with episodic, recurrent symptoms

with or without affective illness, including episodic rage, anger or violence, and self-destructive behavior; such symptoms may be associated with psychotic or nonpsychotic illnesses, personality disorders, organic disorders, or mental retardation

- Lithium is better tolerated during acute manic phases than when manic symptoms have abated
- Adverse effects generally increase in incidence and severity as lithium serum levels increase
- Although not recommended for use in patients with severe renal or cardiovascular disease, dehydration, or sodium depletion, lithium can be administered cautiously in a hospital setting to such patients, with lithium serum levels determined daily
- Lithium-induced weight gain may be more common in women than in men



Suggested Reading

Baldessarini RJ, Tondo L, Davis P, et al. Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. *Bipolar Disord* 2006;8(5 Pt 2):625–39.

Goodwin FK. Rationale for using lithium in combination with other mood stabilizers in the management of bipolar disorder. *J Clin Psychiatry* 2003;64(Suppl 5):S18–24.

Goodwin GM, Bowden CL, Calabrese JR, et al. A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium

maintenance treatment in bipolar I disorder. *J Clin Psychiatry* 2004;65:432–41.

Malhi GS, Tanious M. Optimal frequency of lithium administration in the treatment of bipolar disorder: clinical and dosing considerations. *CNS Drugs* 2011;25(4):289–98.

Tueth MJ, Murphy TK, Evans DL. Special considerations: use of lithium in children, adolescents, and elderly populations. *J Clin Psychiatry* 1998;59(Suppl 6):S66–73.

THERAPEUTICS

- Brands**
- Deprimyl
 - Gamanil

see index for additional brand names

Generic? Yes



Class

- Neuroscience-based Nomenclature: serotonin, norepinephrine reuptake inhibitor (SN-RI)
- Tricyclic antidepressant (TCA)
- Predominantly a norepinephrine/noradrenaline reuptake inhibitor

Commonly Prescribed for

(bold for FDA approved)

- Major depressive disorder
- Anxiety
- Insomnia
- Neuropathic pain/chronic pain
- Treatment-resistant depression



How the Drug Works

- Boosts neurotransmitter norepinephrine/noradrenaline
- Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing noradrenergic neurotransmission
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, lofepramine can increase dopamine neurotransmission in this part of the brain
- A more potent inhibitor of norepinephrine reuptake pump than serotonin reuptake pump (serotonin transporter)
- At high doses may also boost neurotransmitter serotonin and presumably increase serotonergic neurotransmission

How Long Until It Works

- May have immediate effects in treating insomnia or anxiety
- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment of depression is complete remission of current symptoms as well as prevention of future relapses
- The goal of treatment of chronic neuropathic pain is to reduce symptoms as much as possible, especially in combination with other treatments
- Treatment of depression most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Treatment of chronic neuropathic pain may reduce symptoms, but rarely eliminates them completely, and is not a cure since symptoms can recur after medicine is stopped
- Continue treatment of depression until all symptoms are gone (remission)
- Once symptoms of depression are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders and chronic pain may also need to be indefinite, but long-term treatment is not well studied in these conditions

If It Doesn't Work

- Many depressed patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other depressed patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer



Best Augmenting Combos for Partial Response or Treatment Resistance

- Lithium, buspirone, thyroid hormone (for depression)
- Gabapentin, tiagabine, other anticonvulsants, even opiates if done by experts while monitoring carefully in difficult cases (for chronic pain)

Tests

- Baseline ECG is recommended for patients over age 50
- Since tricyclic and tetracyclic antidepressants are frequently associated with weight gain, before starting treatment, weigh all patients and determine if the patient is already overweight (BMI 25.0–29.9) or obese (BMI ≥ 30)
- Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–125 mg/dL), diabetes (fasting plasma glucose > 126 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management
- Monitor weight and BMI during treatment
- While giving a drug to a patient who has gained $> 5\%$ of initial weight, consider evaluating for the presence of pre-diabetes, diabetes, or dyslipidemia, or consider switching to a different antidepressant
- EKGs may be useful for selected patients (e.g., those with personal or family history of QTc prolongation; cardiac arrhythmia; recent myocardial infarction; uncompensated heart failure; or taking agents that prolong QTc interval such as pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin, etc.)
- Patients at risk for electrolyte disturbances (e.g., patients on diuretic therapy) should have baseline and periodic serum potassium and magnesium measurements

SIDE EFFECTS

How Drug Causes Side Effects

- Anticholinergic activity may explain sedative effects, dry mouth, constipation, and blurred vision
- Sedative effects and weight gain may be due to antihistamine properties
- Blockade of alpha adrenergic 1 receptors may explain dizziness, sedation, and hypotension
- Cardiac arrhythmias and seizures, especially in overdose, may be caused by blockade of ion channels

Notable Side Effects

- Blurred vision, constipation, urinary retention, increased appetite, dry mouth, nausea, diarrhea, heartburn, unusual taste in mouth, weight gain
- Fatigue, weakness, dizziness, sedation, headache, anxiety, nervousness, restlessness
- Sexual dysfunction, sweating



Life-Threatening or Dangerous Side Effects

- Paralytic ileus, hyperthermia (TCAs + anticholinergic agents)
- Lowered seizure threshold and rare seizures
- Orthostatic hypotension, sudden death, arrhythmias, tachycardia
- QTc prolongation
- Hepatic failure, extrapyramidal symptoms
- Increased intraocular pressure
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Many experience and/or can be significant in amount
- Can increase appetite and carbohydrate craving

Sedation



- Many experience and/or can be significant in amount
- Tolerance to sedative effect may develop with long-term use

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- Switch to an SSRI or newer antidepressant

Best Augmenting Agents for Side Effects

- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 140–210 mg/day

Dosage Forms

- Tablet 70 mg multiscored
- Liquid 70 mg/5mL

How to Dose

- Initial 70 mg/day once daily or in divided doses; gradually increase daily dose to achieve desired therapeutic effects; dose at bedtime for daytime sedation and in morning for insomnia; maximum dose 280 mg/day for inpatients, 210 mg/day for outpatients



Dosing Tips

- If given in a single dose, should generally be administered at bedtime because of its sedative properties
- If given in split doses, largest dose should generally be given at bedtime because of its sedative properties
- If patients experience nightmares, split dose and do not give large dose at bedtime
- Unusual dose compared to most TCAs
- Patients treated for chronic pain may only require lower doses
- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar

disorder, and switch to a mood stabilizer or an atypical antipsychotic

Overdose

- Death may occur; convulsions, cardiac dysrhythmias, severe hypotension, CNS depression, coma, changes in EKG

Long-Term Use

- Safe

Habit Forming

- No

How to Stop

- Taper to avoid withdrawal effects
- Even with gradual dose reduction some withdrawal symptoms may appear within the first 2 weeks
- Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation
- If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly

Pharmacokinetics

- Substrate for CYP450 2D6
- Half-life of parent compound approximately 1.5–6 hours
- Major metabolite is the antidepressant desipramine, with a half-life of approximately 24 hours



Drug Interactions

- Tramadol increases the risk of seizures in patients taking TCAs
- Use of TCAs with anticholinergic drugs may result in paralytic ileus or hyperthermia
- Fluoxetine, paroxetine, bupropion, duloxetine, and other CYP450 2D6 inhibitors may increase TCA concentrations
- Cimetidine may increase plasma concentrations of TCAs and cause anticholinergic symptoms
- Phenothiazines or haloperidol may raise TCA blood concentrations
- May alter effects of antihypertensive drugs; may inhibit hypotensive effects of clonidine
- Use with sympathomimetic agents may increase sympathetic activity

- Methylphenidate may inhibit metabolism of TCAs
- Activation and agitation, especially following switching or adding antidepressants, may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of lofepramine



Other Warnings/ Precautions

- Add or initiate other antidepressants with caution for up to 2 weeks after discontinuing lofepramine
- Generally, do not use with MAOIs, including 14 days after MAOIs are stopped; do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing lofepramine, but see Pearls
- Use with caution in patients with history of seizure, urinary retention, angle-closure glaucoma, hyperthyroidism
- TCAs can increase QTc interval, especially at toxic doses, which can be attained not only by overdose but also by combining with drugs that inhibit its metabolism via CYP450 2D6, potentially causing torsade de pointes-type arrhythmia or sudden death
- Because TCAs can prolong QTc interval, use with caution in patients who have bradycardia or who are taking drugs that can induce bradycardia (e.g., beta blockers, calcium channel blockers, clonidine, digitalis)
- Because TCAs can prolong QTc interval, use with caution in patients who have hypokalemia and/or hypomagnesemia or who are taking drugs that can induce hypokalemia and/or magnesemia (e.g., diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactide)
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart

- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is recovering from myocardial infarction
- If patient is taking agents capable of significantly prolonging QTc interval (e.g., pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin)
- If there is a history of QTc prolongation or cardiac arrhythmia, recent acute myocardial infarction, uncompensated heart failure
- If patient is taking drugs that inhibit TCA metabolism, including CYP450 2D6 inhibitors, except by an expert
- If there is reduced CYP450 2D6 function, such as patients who are poor 2D6 metabolizers, except by an expert and at low doses
- If there is a proven allergy to lofepramine, desipramine, or imipramine

SPECIAL POPULATIONS

Renal Impairment

- Use with caution

Hepatic Impairment

- Use with caution

Cardiac Impairment

- Baseline ECG is recommended
- TCAs have been reported to cause arrhythmias, prolongation of conduction time, orthostatic hypotension, sinus tachycardia, and heart failure, especially in the diseased heart
- Myocardial infarction and stroke have been reported with TCAs
- TCAs produce QTc prolongation, which may be enhanced by the existence of bradycardia, hypokalemia, congenital or acquired long QTc interval, which should be evaluated prior to administering lofepramine

- Use with caution if treating concomitantly with a medication likely to produce prolonged bradycardia, hypokalemia, slowing of intracardiac conduction, or prolongation of the QTc interval
- Avoid TCAs in patients with a known history of QTc prolongation, recent acute myocardial infarction, and uncompensated heart failure
- TCAs may cause a sustained increase in heart rate in patients with ischemic heart disease and may worsen (decrease) heart rate variability, an independent risk of mortality in cardiac populations
- Since SSRIs may improve (increase) heart rate variability in patients following a myocardial infarct and may improve survival as well as mood in patients with acute angina or following a myocardial infarction, these are more appropriate agents for cardiac population than tricyclic/tetracyclic antidepressants

* Risk/benefit ratio may not justify use of TCAs in cardiac impairment

Elderly

- Baseline ECG is recommended for patients over age 50
- May be more sensitive to anticholinergic, cardiovascular, hypotensive, and sedative effects
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Not recommended for use under age 18
- Several studies show lack of efficacy of TCAs for depression
- May be used to treat enuresis or hyperactive/impulsive behaviors

- Some cases of sudden death have occurred in children taking TCAs



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Crosses the placenta
- Adverse effects have been reported in infants whose mothers took a TCA (lethargy, withdrawal symptoms, fetal malformations)
- Not generally recommended for use during pregnancy, especially during first trimester
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy

Breast Feeding

- Some drug is found in mother's breast milk
- * Recommended either to discontinue drug or bottle feed
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients with insomnia
- Severe or treatment-resistant depression
- Anxious depression

Potential Disadvantages

- Pediatric and geriatric patients
- Patients concerned with weight gain
- Cardiac patients

Primary Target Symptoms

- Depressed mood

**Pearls**

- TCAs are often a first-line treatment option for chronic pain
- TCAs are no longer generally considered a first-line option for depression because of their side effect profile
- TCAs continue to be useful for severe or treatment-resistant depression
- Noradrenergic reuptake inhibitors such as lofepramine can be used as a second-line treatment for smoking cessation, cocaine dependence, and attention deficit disorder
- **Lofepramine is a short-acting prodrug of the TCA desipramine**
- Fewer anticholinergic side effects, particularly sedation, than some other tricyclics
- Once a popular TCA in the UK but not widely marketed throughout the world
- TCAs may aggravate psychotic symptoms
- Alcohol should be avoided because of additive CNS effects
- Underweight patients may be more susceptible to adverse cardiovascular effects
- Children, patients with inadequate hydration, and patients with cardiac disease may be more susceptible to TCA-induced cardiotoxicity than healthy adults
- For the expert only: although generally prohibited, a heroic treatment (but potentially dangerous) for severely treatment-resistant patients is to give a tricyclic/tetracyclic antidepressant other

than clomipramine simultaneously with an MAOI for patients who fail to respond to numerous other antidepressants

- If this option is elected, start the MAOI with the tricyclic/tetracyclic antidepressant simultaneously at low doses after appropriate drug washout, then alternately increase doses of these agents every few days to a week as tolerated
- Although very strict dietary and concomitant drug restrictions must be observed to prevent hypertensive crises and serotonin syndrome, the most common side effects of MAOI/tricyclic or tetracyclic combinations may be weight gain and orthostatic hypotension
- Patients on TCAs should be aware that they may experience symptoms such as photosensitivity or blue-green urine
- SSRIs may be more effective than TCAs in women, and TCAs may be more effective than SSRIs in men
- Since tricyclic/tetracyclic antidepressants are substrates for CYP450 2D6, and 7% of the population (especially Caucasians) may have a genetic variant leading to reduced activity of 2D6, such patients may not safely tolerate normal doses of tricyclic/tetracyclic antidepressants and may require dose reduction
- Phenotypic testing may be necessary to detect this genetic variant prior to dosing with a tricyclic/tetracyclic antidepressant, especially in vulnerable populations such as children, elderly, cardiac populations, and those on concomitant medications
- Patients who seem to have extraordinarily severe side effects at normal or low doses may have this phenotypic CYP450 2D6 variant and require low doses or switching to another antidepressant not metabolized by 2D6

**Suggested Reading**

Anderson IM. Meta-analytical studies on new antidepressants. *Br Med Bull* 2001;57:161–78.

Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *J Aff Disorders* 2000;58:19–36.

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antidepressant lofepramine. *J Int Med Res* 1991;19:183–201.

Lancaster SG, Gonzales JP. Lofepramine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depressive illness. *Drugs* 1989;37:123–40.

THERAPEUTICS

Brands • LATUDA

see index for additional brand names

Generic? No**Class**

- Neuroscience-based Nomenclature: dopamine, serotonin receptor antagonist (DS-RAn)
- Atypical antipsychotic (serotonin-dopamine antagonist; second generation antipsychotic; also a potential mood stabilizer)

Commonly Prescribed for

(bold for FDA approved)

- **Schizophrenia (ages 13 and older)**
- **Bipolar depression**
- Acute mania/mixed mania
- Other psychotic disorders
- Bipolar maintenance
- Treatment-resistant depression
- Behavioral disturbances in dementia
- Behavioral disturbances in children and adolescents
- Disorders associated with problems with impulse control

**How the Drug Works**

- Blocks dopamine 2 receptors, reducing positive symptoms of psychosis and stabilizing affective symptoms
- Blocks serotonin 2A receptors, causing enhancement of dopamine release in certain brain regions and thus reducing motor side effects and possibly improving cognition and affective symptoms
- Potently blocks serotonin 7 receptors, which may be beneficial for mood, sleep, cognitive impairment, and negative symptoms in schizophrenia, and also in bipolar disorder and major depressive disorder
- Partial agonist at 5HT1A receptors, and antagonist actions at serotonin 7 and alpha 2A and alpha 2C receptors, which may be beneficial for mood, anxiety and cognition in a number of disorders
- Lacks potent actions at dopamine D1, muscarinic M1, and histamine H1 receptors, theoretically suggesting less propensity for inducing cognitive

impairment, weight gain, or sedation compared to other agents with these properties

How Long Until It Works

- Psychotic symptoms can improve within 1 week, but it may take several weeks for full effect on behavior as well as on cognition
- Classically recommended to wait at least 4–6 weeks to determine efficacy of drug, but in practice some patients may require up to 16–20 weeks to show a good response, especially on cognitive impairment and functional outcome

If It Works

- Most often reduces positive symptoms but does not eliminate them
- Can improve negative symptoms, as well as aggressive, cognitive, and affective symptoms in schizophrenia
- Most schizophrenia patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third
- Perhaps 5–15% of schizophrenia patients can experience an overall improvement of greater than 50–60%, especially when receiving stable treatment for more than a year
- Such patients are considered super-responders or “awakeners” since they may be well enough to be employed, live independently, and sustain long-term relationships
- Continue treatment until reaching a plateau of improvement
- After reaching a satisfactory plateau, continue treatment for at least a year after first episode of psychosis
- For second and subsequent episodes of psychosis, treatment may need to be indefinite
- Even for first episodes of psychosis, it may be preferable to continue treatment

If It Doesn't Work

- Try one of the other atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, asenapine, iloperidone, amisulpride)
- If 2 or more antipsychotic monotherapies do not work, consider clozapine
- Some patients may require treatment with a conventional antipsychotic

- If no first-line atypical antipsychotic is effective, consider higher doses or augmentation with valproate or lamotrigine
- Consider noncompliance and switch to another antipsychotic with fewer side effects or to an antipsychotic that can be given by depot injection
- Consider initiating rehabilitation and psychotherapy
- Consider presence of concomitant drug abuse



Best Augmenting Combos for Partial Response or Treatment Resistance

- Valproic acid (valproate, divalproex, divalproex ER)
- Mood-stabilizing anticonvulsants (see drug interactions)
- Lithium
- Benzodiazepines

Tests

Before starting any atypical antipsychotic

- Weigh all patients and track BMI during treatment
- Get baseline personal and family history of diabetes, obesity, dyslipidemia, hypertension, and cardiovascular disease
- Get waist circumference (at umbilicus), blood pressure, fasting plasma glucose, and fasting lipid profile
- Determine if the patient is
 - overweight (BMI 25.0–29.9)
 - obese (BMI ≥ 30)
 - has pre-diabetes (fasting plasma glucose 100–125 mg/dL)
 - has diabetes (fasting plasma glucose ≥ 126 mg/dL)
 - has hypertension (BP $>140/90$ mm Hg)
 - has dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol)
- Treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management

Monitoring after starting any atypical antipsychotic

- BMI monthly for 3 months, then quarterly
- Consider monitoring fasting triglycerides monthly for several months in patients at

high risk for metabolic complications and when initiating or switching antipsychotics

- Blood pressure, fasting plasma glucose, fasting lipids within 3 months and then annually, but earlier and more frequently for patients with diabetes or who have gained $>5\%$ of initial weight
- Treat or refer for treatment and consider switching to another atypical antipsychotic for patients who become overweight, obese, pre-diabetic, diabetic, hypertensive, or dyslipidemic while receiving an atypical antipsychotic
- Even in patients without known diabetes, be vigilant for the rare but life-threatening onset of diabetic ketoacidosis, which always requires immediate treatment, by monitoring for the rapid onset of polyuria, polydipsia, weight loss, nausea, vomiting, dehydration, rapid respiration, weakness, and clouding of sensorium, even coma
- Patients with low white blood cell count (WBC) or history of drug-induced leucopenia/neutropenia should have complete blood count (CBC) monitored frequently during the first few months and lurasidone should be discontinued at the first sign of decline in WBC in the absence of other causative factors (class warning)

SIDE EFFECTS

How Drug Causes Side Effects (Class effects)

- By blocking dopamine 2 receptors in the striatum, it can cause motor side effects
- By blocking dopamine 2 receptors in the pituitary, it can cause elevations in prolactin
- Mechanism of weight gain and increased incidence of diabetes and dyslipidemia with atypical antipsychotics is unknown

Notable Side Effects

- Dose-dependent sedation
- Akathisia
- Nausea
- Dose-dependent hyperprolactinemia
- May increase risk for diabetes and dyslipidemia
- Rare tardive dyskinesia (much reduced risk compared to conventional antipsychotics)



Life-Threatening or Dangerous Side Effects

- Tachycardia, first-degree AV block
- Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking atypical antipsychotics (class warning)
- Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis (class warning)
- Rare neuroleptic malignant syndrome (much reduced risk compared to conventional antipsychotics) (class warning)
- Rare seizures (class warning)

Weight Gain

Short Term



- Many experience about one- to two-pound weight gain greater than placebo in short term 6-week trials

Long Term



- Patients in long-term 52-week trials actually lost 1.5 pounds on average
- Clinical experience, however, is still limited
- Appears to be less weight gain than observed with some antipsychotics
- Many patients lost weight in long-term trials when switching from olanzapine to lurasidone

Sedation



- May be higher in short-term trials than in long-term use

What to Do About Side Effects

- Wait
- Wait
- Wait
- Anticholinergics may reduce motor side effects when present
- Dose reduction may reduce akathisia when present
- Consider changing to nighttime dosing (with evening meal)

- Weight loss, exercise programs, and medical management for high BMIs, diabetes, dyslipidemia
- Switch to another atypical antipsychotic

Best Augmenting Agents for Side Effects

- Benztrapine or trihexyphenidyl for motor side effects
- Beta blockers or benzodiazepines may reduce akathisia when present
- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 40–80 mg/day for schizophrenia
- Some patients with schizophrenia may benefit from doses up to 160 mg/day
- 20–60 mg/day for bipolar depression
- Some patients with bipolar depression may benefit from doses up to 120 mg/day

Dosage Forms

- Tablet 20 mg, 40 mg, 60 mg, 80 mg, 120 mg

How to Dose

- Initial 40–80 mg once daily with food for schizophrenia
- Dose titration to initial dose of 40 mg/day is not required for schizophrenia
- Consider dose increases from 40 mg/day up to 160 mg/day as necessary and as tolerated for schizophrenia
- Initial 20 mg once daily with food for bipolar depression
- Can titrate to 120 mg/day in bipolar depression if necessary and tolerated



Dosing Tips

- Lurasidone should be taken with food (i.e., at least a small meal of a minimum of 350 calories)
- Lurasidone absorption can be decreased by up to 50% on an empty stomach and more consistent efficacy will be seen if dosing is done regularly with food
- Once daily dosing
- Giving lurasidone at bedtime can greatly reduce daytime sedation, akathisia, and EPS

- Starting dose for schizophrenia is 40 mg/day, which may be an adequate dose for some patients, especially first-episode and early-onset psychosis cases
- 40–80 mg per day was suggested by controlled clinical trials as adequate for many patients with schizophrenia
- Some patients with schizophrenia benefit from higher dosing, with controlled clinical trials up to 160 mg/day
- Higher doses than 160 mg/day may benefit more difficult patients with schizophrenia with treatment nonresponsiveness to other agents
- Higher dosing, however, may cause more side effects
- Dosing for bipolar depression or major depressive episodes with mixed features is generally lower than for schizophrenia, with a 20 mg starting dose; 20 mg/day may be an adequate dose for some patients
- Doses between 20 and 60 mg/day are generally as efficacious as doses between 60 and 120 mg/day for bipolar depression or major depressive episodes with mixed features
- Some patients with bipolar depression or major depressive episodes with mixed features may require higher doses

Overdose

- Limited data

Long-Term Use

- Not extensively studied past 52 weeks, but long-term maintenance treatment is often necessary for schizophrenia
- Should periodically reevaluate long-term usefulness in individual patients, but treatment may need to continue for many years in patients with schizophrenia

Habit Forming

- No

How to Stop

- Down-titration, especially when simultaneously beginning a new antipsychotic while switching (i.e., cross-titration)
- Rapid discontinuation could theoretically lead to rebound psychosis and worsening of symptoms

Pharmacokinetics

- Half-life 18–31 hours (shorter half-life better documented at the 40 mg dose)
- Metabolized by CYP450 3A4
- Cmax and bioavailability are reduced if taken without food



Drug Interactions

- Inhibitors of CYP450 3A4 (e.g., nefazodone, fluvoxamine, fluoxetine, ketoconazole) may increase plasma levels of lurasidone
- Coadministration of lurasidone with a strong CYP450 3A4 inhibitor (e.g., ketoconazole) or with a strong CYP450 3A4 inducer (e.g., rifampin) is contraindicated
- Coadministration of lurasidone with moderate CYP450 3A4 inhibitors can be considered; recommended starting dose is 20 mg/day; recommended maximum dose is 80 mg/day
- Moderate inducers of CYP450 3A4 may decrease plasma levels of lurasidone
- May increase effects of antihypertensive agents
- May antagonize levodopa, dopamine agonists



Other Warnings/ Precautions

- Use with caution in patients with conditions that predispose to hypotension (dehydration, overheating)
- Dysphagia has been associated with antipsychotic use, and lurasidone should be used cautiously in patients at risk for aspiration pneumonia

Do Not Use

- If patient is taking a strong CYP 3A4 inhibitor (e.g., ketoconazole) or inducer (e.g., rifampin)
- In patients with a history of angioedema
- If there is a proven allergy to lurasidone

SPECIAL POPULATIONS

Renal Impairment

- Moderate and severe impairment: initial 20 mg/day; maximum dose 80 mg/day

Hepatic Impairment

- Moderate impairment: initial 20 mg/day; maximum dose 80 mg/day
- Severe impairment: initial 20 mg/day; maximum dose 40 mg/day

Cardiac Impairment

- Should be used with caution because of theoretical risk of orthostatic hypotension, although low potency at alpha 1 receptors suggests this risk may be less than for some other antipsychotics
- Lurasidone does not have a warning for QTc prolongation

Elderly

- In general, no dose adjustment is necessary for elderly patients
- However, some elderly patients may tolerate lower doses better
- Although atypical antipsychotics are commonly used for behavioral disturbances in dementia, no agent has been approved for treatment of elderly patients with dementia-related psychosis
- Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo, and also have an increased risk of cerebrovascular events



Children and Adolescents

- Safety and efficacy have not been established
- Children and adolescents using lurasidone may need to be monitored more often than adults



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Animal studies do not show adverse effects

- There is a risk of abnormal muscle movements and withdrawal symptoms in newborns whose mothers took an antipsychotic during the third trimester; symptoms may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty feeding
- Psychotic symptoms may worsen during pregnancy and some form of treatment may be necessary
- Lurasidone may be preferable to anticonvulsant mood stabilizers if treatment is required during pregnancy
- National Pregnancy Registry for Atypical Antipsychotics: 1-866-961-2388 or <http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/>

Breast Feeding

- Unknown if lurasidone is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- Recommended either to discontinue drug or bottle feed unless the potential benefit to the mother justifies the potential risk to the child
- Intants of women who choose to breast feed while on lurasidone should be monitored for possible adverse effects

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients requiring rapid onset of antipsychotic action without dosage titration
- Patients who wish to take an antipsychotic once a day
- Patients experiencing weight gain from other antipsychotics or who wish to avoid weight gain

Potential Disadvantages

- Patients who cannot take a medication consistently with food

Primary Target Symptoms

- Positive symptoms of psychosis
- Negative symptoms of psychosis
- Cognitive symptoms
- Unstable mood (both depression and mania)
- Aggressive symptoms



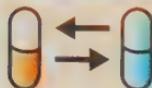
Pearls

- Clinical trials suggest that lurasidone is well tolerated with a favorable balance of efficacy and safety
- One of the few “metabolically friendly” antipsychotics
 - Neutral for weight gain (1–2 pounds weight gain in short-term studies, with 1–2 pounds weight loss in long-term studies)
 - Neutral for lipids (triglycerides and cholesterol)
 - Neutral for glucose
- Only atypical antipsychotic documented not to cause QTc prolongation, and one of the few atypical antipsychotics without a QTc warning
- Seems to have low-level EPS, especially when dosed at bedtime
- Somnolence and akathisia are the most common side effects in short-term clinical trials of schizophrenia that dosed lurasidone in the daytime, but these adverse effects were reduced in a controlled study of lurasidone administered at night with food
- Nausea and occasional vomiting occurred in bipolar depression studies especially at higher doses
- Nausea and vomiting generally rapidly abates within a few days or can be avoided by slow dose titration and giving lower doses
- Prolactin elevations low and generally transient
- Agitation experienced by some patients
- Receptor binding profile suggests favorable potential as an antidepressant
 - 5HT7 antagonism is antidepressant in animal models and has pro-cognitive actions in animal models
 - 5HT7 antagonism and 5HT1A partial agonism enhance serotonin levels in animals treated with SSRIs/SNRIs,

suggesting use for lurasidone as an augmenting agent to SSRIs/SNRIs in depression

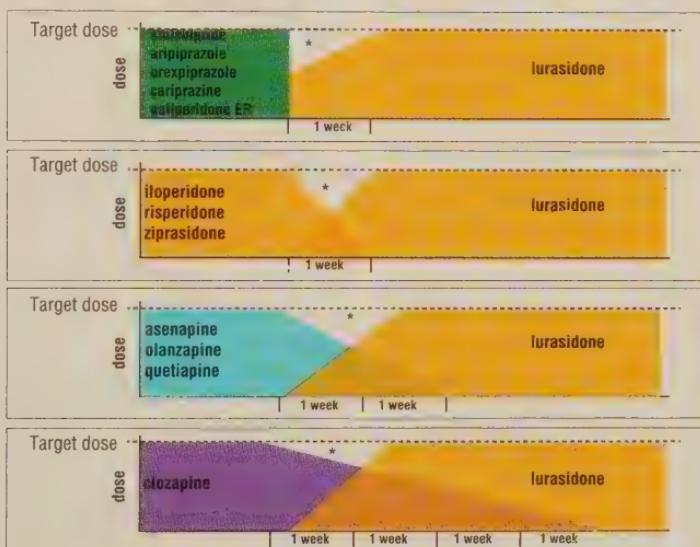
- 5HT7 antagonism plus the absence of D1, H1, and M1 antagonism suggest potential for cognitive improvement
- Lack of D1 antagonist, anticholinergic, and antihistamine properties may explain relative lack of cognitive side effects in most patients
- One of the best studied agents for depression with mixed features, showing efficacy in a large randomized controlled trial
- Not approved for mania, but almost all atypical antipsychotics approved for acute treatment of schizophrenia have proven effective in the acute treatment of mania as well
- Patients with inadequate responses to atypical antipsychotics may benefit from determination of plasma drug levels and, if low, a dosage increase even beyond the usual prescribing limits
- Patients with inadequate responses to atypical antipsychotics may also benefit from a trial of augmentation with a conventional antipsychotic or switching to a conventional antipsychotic
- However, long-term polypharmacy with a combination of a conventional antipsychotic with an atypical antipsychotic may combine their side effects without clearly augmenting the efficacy of either
- For treatment-resistant patients, especially those with impulsivity, aggression, violence, and self-harm, long-term polypharmacy with 2 atypical antipsychotics or with 1 atypical antipsychotic and 1 conventional antipsychotic may be useful or even necessary while closely monitoring
- In such cases, it may be beneficial to combine 1 depot antipsychotic with 1 oral antipsychotic

THE ART OF SWITCHING



Switching from Oral Antipsychotics to Lurasidone

- With aripiprazole, amisulpride, and paliperidone ER, immediate stop is possible; begin lurasidone at an intermediate dose
- Clinical experience has shown that quetiapine, olanzapine, and asenapine should be tapered off slowly over a period of 3–4 weeks, to allow patients to readapt to the withdrawal of blocking cholinergic, histaminergic, and alpha-1 receptors
- Clozapine should always be tapered off slowly, over a period of 4 weeks or more
- Benzodiazepine or anticholinergic medication can be administered during cross-titration to help alleviate side effects such as insomnia, agitation, and/or psychosis



Suggested Reading

Ishibashi T, Horisawa T, Tokuda K, et al. Pharmacological profile of lurasidone, a novel antipsychotic agent with potent 5-hydroxytryptamine 7 (5-HT7) and 5-HT1A receptor activity. *J Pharmacol Exp Ther* 2010;334(1):171–81.

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THERAPEUTICS

Brands • Ludiomil

see index for additional brand names

Generic? Yes**Class**

- Neuroscience-based Nomenclature: norepinephrine reuptake inhibitor (N-RI)
- Tricyclic antidepressant (TCA), sometimes classified as a tetracyclic antidepressant (tetra)
- Predominantly a norepinephrine/noradrenaline reuptake inhibitor

Commonly Prescribed for

(bold for FDA approved)

- **Depression**
- Anxiety
- Insomnia
- Neuropathic pain/chronic pain
- Treatment-resistant depression

**How the Drug Works**

- Boosts neurotransmitter norepinephrine/noradrenaline
- Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing noradrenergic neurotransmission
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, maprotiline can thus increase dopamine neurotransmission in this part of the brain
- A more potent inhibitor of norepinephrine reuptake pump than serotonin reuptake pump (serotonin transporter)
- At high doses may also boost neurotransmitter serotonin and presumably increase serotonergic neurotransmission

How Long Until It Works

- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment of depression is complete remission of current symptoms as well as prevention of future relapses
- The goal of treatment of chronic neuropathic pain is to reduce symptoms as much as possible, especially in combination with other treatments
- Treatment of depression most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine is stopped
- Treatment of chronic neuropathic pain may reduce symptoms, but rarely eliminates them completely, and is not a cure since symptoms can recur after medicine is stopped
- Continue treatment of depression until all symptoms are gone (remission)
- Once symptoms of depression are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders and chronic pain may also need to be indefinite, but long-term treatment is not well studied in these conditions

If It Doesn't Work

- Many depressed patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other depressed patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer



Best Augmenting Combos for Partial Response or Treatment Resistance

- Lithium, buspirone, thyroid hormone (for depression)
- Gabapentin, tiagabine, other anticonvulsants, even opiates if done by experts while monitoring carefully in difficult cases (for chronic pain)

Tests

- Baseline ECG is recommended for patients over age 50
- Since tricyclic and tetracyclic antidepressants are frequently associated with weight gain, before starting treatment, weigh all patients and determine if the patient is already overweight (BMI 25.0–29.9) or obese (BMI ≥ 30)
- Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–125 mg/dL), diabetes (fasting plasma glucose >126 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management
- Monitor weight and BMI during treatment
- While giving a drug to a patient who has gained $>5\%$ of initial weight, consider evaluating for the presence of pre-diabetes, diabetes, or dyslipidemia, or consider switching to a different antidepressant
- EKGs may be useful for selected patients (e.g., those with personal or family history of QTc prolongation; cardiac arrhythmia; recent myocardial infarction; uncompensated heart failure; or taking agents that prolong QTc interval such as pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin, etc.)
- Patients at risk for electrolyte disturbances (e.g., patients on diuretic therapy) should have baseline and periodic serum potassium and magnesium measurements

SIDE EFFECTS

How Drug Causes Side Effects

- Anticholinergic activity may explain sedative effects, dry mouth, constipation, and blurred vision
- Sedative effects and weight gain may be due to antihistamine properties
- Blockade of alpha adrenergic 1 receptors may explain dizziness, sedation, and hypotension
- Cardiac arrhythmias and seizures, especially in overdose, may be caused by blockade of ion channels

Notable Side Effects

- Blurred vision, constipation, urinary retention, increased appetite, dry mouth, nausea, diarrhea, heartburn, unusual taste in mouth, weight gain
- Fatigue, weakness, dizziness, sedation, headache, anxiety, nervousness, restlessness
- Sexual dysfunction (impotence, change in libido)
- Sweating, rash, itching



Life-Threatening or Dangerous Side Effects

- Paralytic ileus, hyperthermia (TCAs/tetracyclics + anticholinergic agents)
- Lowered seizure threshold and rare seizures
- Orthostatic hypotension, sudden death, arrhythmias, tachycardia
- QTc prolongation
- Hepatic failure, extrapyramidal symptoms
- Increased intraocular pressure
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Many experience and/or can be significant in amount
- Can increase appetite and carbohydrate craving

Sedation



- Many experience and/or can be significant in amount
- Tolerance to sedative effect may develop with long-term use

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- Switch to an SSRI or newer antidepressant

Best Augmenting Agents for Side Effects

- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 75–150 mg/day (for depression)
- 50–150 mg/day (for chronic pain)

Dosage Forms

- Tablet 25 mg, 50 mg, 75 mg

How to Dose

- Initial 25 mg/day at bedtime; increase by 25 mg every 3–7 days
- 75 mg/day; after 2 weeks increase dose gradually by 25 mg/day; maximum dose generally 225 mg/day



Dosing Tips

- If given in a single dose, should generally be administered at bedtime because of its sedative properties
- If given in split doses, largest dose should generally be given at bedtime because of its sedative properties
- If patients experience nightmares, split dose and do not give large dose at bedtime
- Patients treated for chronic pain may only require lower doses
- Risk of seizures increases with dose, especially with maprotiline above 200 mg/day
- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon

dosing initiation or discontinuation, consider the possibility of activated bipolar disorder, and switch to a mood stabilizer or an atypical antipsychotic

Overdose

- Death may occur; convulsions, cardiac dysrhythmias, severe hypotension, CNS depression, coma, changes in EKG

Long-Term Use

- Safe

Habit Forming

- No

How to Stop

- Taper to avoid withdrawal effects
- Even with gradual dose reduction some withdrawal symptoms may appear within the first 2 weeks
- Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation
- If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly

Pharmacokinetics

- Substrate for CYP450 2D6
- Mean half-life approximately 51 hours
- Peak plasma concentration 8–24 hours



Drug Interactions

- Tramadol increases the risk of seizures in patients taking TCAs
- Use of TCAs/tetracyclines with anticholinergic drugs may result in paralytic ileus or hyperthermia
- Fluoxetine, paroxetine, bupropion, duloxetine, and other CYP450 2D6 inhibitors may increase TCA/tetracyclic concentrations
- Cimetidine may increase plasma concentrations of TCAs/tetracyclines and cause anticholinergic symptoms
- Phenothiazines or haloperidol may raise TCA/tetracyclic blood concentrations
- May alter effects of antihypertensive drugs; may inhibit hypotensive effects of clonidine
- Use with sympathomimetic agents may increase sympathetic activity

- Methylphenidate may inhibit metabolism of TCAs/tetracyclines
- Activation and agitation, especially following switching or adding antidepressants, may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of maprotiline



Other Warnings/ Precautions

- Add or initiate other antidepressants with caution for up to 2 weeks after discontinuing maprotiline
- Generally, do not use with MAOIs, including 14 days after MAOIs are stopped; do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing maprotiline, but see Pearls
- Use with caution in patients with history of seizures, urinary retention, angle-closure glaucoma, hyperthyroidism
- TCAs/tetracyclines can increase QTc interval, especially at toxic doses, which can be attained not only by overdose but also by combining with drugs that inhibit TCA/tetracyclic metabolism via CYP450 2D6, potentially causing torsade de pointes-type arrhythmia or sudden death
- Because TCAs/tetracyclines can prolong QTc interval, use with caution in patients who have bradycardia or who are taking drugs that can induce bradycardia (e.g., beta blockers, calcium channel blockers, clonidine, digitalis)
- Because TCAs/tetracyclines can prolong QTc interval, use with caution in patients who have hypokalemia and/or hypomagnesemia or who are taking drugs that can induce hypokalemia and/or magnesemia (e.g., diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactide)
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart

- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is recovering from myocardial infarction
- If patient is taking agents capable of significantly prolonging QTc interval (e.g., pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin)
- If there is a history of QTc prolongation or cardiac arrhythmia, recent acute myocardial infarction, uncompensated heart failure
- If patient is taking drugs that inhibit TCA/tetracyclic metabolism, including CYP450 2D6 inhibitors, except by an expert
- If there is reduced CYP450 2D6 function, such as patients who are poor 2D6 metabolizers, except by an expert and at low doses
- If there is a proven allergy to maprotiline

SPECIAL POPULATIONS

Renal Impairment

- Use with caution

Hepatic Impairment

- Use with caution

Cardiac Impairment

- Baseline ECG is recommended
- TCAs/tetracyclines have been reported to cause arrhythmias, prolongation of conduction time, orthostatic hypotension, sinus tachycardia, and heart failure, especially in the diseased heart
- Myocardial infarction and stroke have been reported with TCAs/tetracyclines
- TCAs/tetracyclines produce QTc prolongation, which may be enhanced by the existence of bradycardia, hypokalemia, congenital or acquired long QTc interval, which should be evaluated prior to administering maprotiline
- Use with caution if treating concomitantly with a medication likely to produce

- prolonged bradycardia, hypokalemia, slowing of intracardiac conduction, or prolongation of the QTc interval
 - Avoid TCAs/tetracyclines in patients with a known history of QTc prolongation, recent acute myocardial infarction, and uncompensated heart failure
 - TCAs/tetracyclines may cause a sustained increase in heart rate in patients with ischemic heart disease and may worsen (decrease) heart rate variability, an independent risk of mortality in cardiac populations
 - Since SSRIs may improve (increase) heart rate variability in patients following a myocardial infarct and may improve survival as well as mood in patients with acute angina or following a myocardial infarction, these are more appropriate agents for cardiac population than tricyclic/tetracyclic antidepressants
- * Risk/benefit ratio may not justify use of TCAs/tetracyclines in cardiac impairment

Elderly

- Baseline ECG is recommended for patients over age 50
- May be more sensitive to anticholinergic, cardiovascular, hypotensive, and sedative effects
- Usual dose generally 50–75 mg/day
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Not recommended for use under age 18
- Several studies show lack of efficacy of TCAs/tetracyclines for depression

- May be used to treat enuresis or hyperactive/impulsive behaviors
- Some cases of sudden death have occurred in children taking TCAs/tetracyclines
- Maximum dose for children and adolescents is 75 mg/day



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLL or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Animal studies do not show adverse effects
- Adverse effects have been reported in infants whose mothers took a TCA/tetracyclic (lethargy, withdrawal symptoms, fetal malformations)
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy

Breast Feeding

- Some drug is found in mother's breast milk
- * Recommended either to discontinue drug or bottle feed
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients with insomnia
- Severe or treatment-resistant depression

Potential Disadvantages

- Pediatric and geriatric patients
- Patients concerned with weight gain
- Cardiac patients
- Patients with seizure disorders

Primary Target Symptoms

- Depressed mood
- Chronic pain



Pearls

- Tricyclic/tetracyclic antidepressants are often a first-line treatment option for chronic pain
- Tricyclic/tetracyclic antidepressants are no longer generally considered a first-line treatment option for depression because of their side effect profile
- Tricyclic/tetracyclic antidepressants continue to be useful for severe or treatment-resistant depression
- Tricyclic/tetracyclic antidepressants may have somewhat increased risk of seizures compared to some other TCAs, especially at higher doses
- TCAs/tetracyclines may aggravate psychotic symptoms
- Alcohol should be avoided because of additive CNS effects
- Underweight patients may be more susceptible to adverse cardiovascular effects
- Children, patients with inadequate hydration, and patients with cardiac disease may be more susceptible to TCA/tetracyclic-induced cardiotoxicity than healthy adults
- For the expert only: a heroic treatment (but potentially dangerous) for severely treatment-resistant patients is to give simultaneously with MAOIs for patients

who fail to respond to numerous other antidepressants

- If this option is elected, start the MAOI with the tricyclic/tetracyclic antidepressant simultaneously at low doses after appropriate drug washout, then alternately increase doses of these agents every few days to a week as tolerated
- Although very strict dietary and concomitant drug restrictions must be observed to prevent hypertensive crises and serotonin syndrome, the most common side effects of MAOI/tricyclic or tetracyclic combinations may be weight gain and orthostatic hypotension
- Patients on tricyclics/tetracyclics should be aware that they may experience symptoms such as photosensitivity or blue-green urine
- SSRIs may be more effective than TCAs/tetracyclines in women, and TCAs/tetracyclines may be more effective than SSRIs in men
- May have a more rapid onset of action than some other TCAs/tetracyclines
- Since tricyclic/tetracyclic antidepressants are substrates for CYP450 2D6, and 7% of the population (especially Caucasians) may have a genetic variant leading to reduced activity of 2D6, such patients may not safely tolerate normal doses of tricyclic/tetracyclic antidepressants and may require dose reduction
- Phenotypic testing may be necessary to detect this genetic variant prior to dosing with a tricyclic/tetracyclic antidepressant, especially in vulnerable populations such as children, elderly, cardiac populations, and those on concomitant medications
- Patients who seem to have extraordinarily severe side effects at normal or low doses may have this phenotypic CYP450 2D6 variant and require low doses or switching to another antidepressant not metabolized by 2D6



Suggested Reading

Anderson IM. Meta-analytical studies on new antidepressants. *Br Med Bull* 2001;57:161–78.

Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *J Aff Disorders* 2000;58:19–36.

Kane JM, Lieberman J. The efficacy of amoxapine, maprotiline, and trazodone in comparison to imipramine and amitriptyline: a review of the literature. *Psychopharmacol Bull* 1984;20:240–9.

THERAPEUTICS

Brands • Deplin

see index for additional brand names

Generic? No



Class

- Medical food (bioavailable form of folate)
- Trimonoamine modulator

Commonly Prescribed for

(bold for FDA approved as medical food indications)

- Suboptimal folate levels in depressed patients (**adjunct to antidepressant**)
- Hyperhomocysteinemia in schizophrenia patients (**adjunct to antipsychotic**)
- Enhancement of antidepressant response at the initiation of treatment
- Cognitive or mood symptoms in patients with MTHFR (methylene tetrahydrofolate) deficiency



How the Drug Works

- Folate is a water-soluble B vitamin (B9) that is essential for cell growth/reproduction, breakdown/utilization of proteins, formation of nucleic acids, and other functions
- L-methylfolate, or 6-(S)-5-methyl-tetrahydrofolate, is derived from folate and is the form that enters the brain and works directly as a methyl donor and monoamine synthesis modulator
- That is, it regulates tetrahydrobiopterin (BH4), a critical enzyme cofactor for trimonoamine neurotransmitter synthesis
- Methyl donor for DNA methylation and thus an epigenetic regulator

How Long Until It Works

- Onset of therapeutic actions in depression is usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment for depression is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine is stopped
- Continue treatment until all symptoms are gone (remission)
- Once symptoms gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite

If It Doesn't Work

- Many patients with depression have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer



Best Augmenting Combos for Partial Response or Treatment Resistance

- L-methylfolate is itself an adjunct to standard treatments for depression or schizophrenia at the initiation of treatment or to augment a partial response

Tests

- Baseline folate levels (serum levels for recent folate intake; red blood cell or CSF levels for long-term folate levels)
- Baseline homocysteine levels (reciprocal relationship with folate levels; high homocysteine levels may be more sensitive in detected folate deficiency than folate levels themselves in some patients)

- May monitor folate levels for patients taking an agent capable of affecting folate metabolism, absorption, or degradation
- May consider genotyping for deficient folate synthesis via MTHFR T alleles or MTHFD1 A alleles

SIDE EFFECTS

How Drug Causes Side Effects

- L-methylfolate does not typically cause side effects

Notable Side Effects

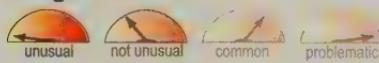
- L-methylfolate does not typically cause side effects



Life-Threatening or Dangerous Side Effects

- Theoretically, rare induction of mania or suicidal ideation and behavior (suicidality)

Weight Gain



- Reported but not expected

Sedation



- Reported but not expected

What to Do About Side Effects

- Wait
- Lower the dose or administer in divided doses
- Switch to another drug

Best Augmenting Agents for Side Effects

- Many side effects cannot be improved with an augmenting agent
- Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of L-methylfolate or the primary antidepressant

DOSING AND USE

Usual Dosage Range

- 7.5–15 mg/day

Dosage Forms

- Tablet 7.5 mg, 15 mg

How to Dose

- Initial 7.5–15 mg/day
- Doses above 15 mg/day should be administered in divided doses



Dosing Tips

- Can be taken with or without food
- L-methyltetrahydrofolate was shown to be 7 times more bioavailable than folic acid
- That means 7.5 mg of the active L enantiomer of methylfolate may be equivalent to 52 mg of folate (usual dose of folate is 100 µg to 1.0 mg)
- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar disorder and switch to a mood stabilizer or an atypical antipsychotic

Overdose

- Doses up to 90 mg/day of methylfolate (45 mg L-methylfolate) have been studied without any additional adverse events
- L-methylfolate is generally regarded as safe
- A toxic dose of L-methylfolate is not known at this time

Long-Term Use

- Safe

Habit Forming

- No

How to Stop

- Taper not necessary

Pharmacokinetics

- Mean elimination half-life approximately 3 hours for d,L-methylfolate
- L-methylfolate is naturally stored in most cells and used by the body when needed; therefore, L-methylfolate may not follow typical drug pharmacokinetic patterns



Drug Interactions

- L-methylfolate may reduce plasma levels of certain anticonvulsants, including phenytoin, carbamazepine, fosphenytoin, phenobarbital, primidone, or valproate
- L-methylfolate may reduce plasma levels of pyrimethamine
- Patients taking folate-lowering drugs (e.g., anticonvulsants, cholestyramine, colestipol, cycloserine, aminopterin, methotrexate, sulfasalazine, pyrimethamine, triamterene, trimethoprim, isotretinoin, fluoxetine, nonsteroidal anti-inflammatory drugs (NSAIDs), methylprednisolone, pentamidine, or who smoke or drink heavily may require higher doses of L-methylfolate



Other Warnings/ Precautions

- Folic acid may mask symptoms of B12 deficiency (e.g., pernicious anemia), although this may be less likely with L-methylfolate
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- Monitor patients for activation of suicidal ideation, especially children and adolescents
- Folic acid, when administered in doses above 800 mcg, may increase the amount of unmetabolized folic acid, which has been linked to accelerated growth of existing neoplasms in the colon; L-methylfolate may be less likely than folic acid to accelerate the growth of existing neoplasms

Do Not Use

- If there is a proven allergy to folate or folic acid

SPECIAL POPULATIONS

Renal Impairment

- Dose adjustment not necessary

Hepatic Impairment

- Dose adjustment not necessary

Cardiac Impairment

- Dose adjustment not necessary

Elderly

- Dose adjustment not necessary



Children and Adolescents

- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Safety and efficacy have not been established



Pregnancy

- No controlled studies in humans or animals
- Controlled studies of folic acid at recommended doses have failed to demonstrate risk to the fetus
- There are no studies of folic acid at high doses
- Because pregnant women are advised to take folic acid or prenatal vitamins that contain folic acid, it is important to ask the patient about any supplements or vitamins she may be taking and consider this when deciding whether to prescribe L-methylfolate

Breast Feeding

- Some drug is found in mother's breast milk

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients who need efficacy greater than an antidepressant alone at the initiation of treatment
- Patients with partial or inadequate response to antidepressants
- Patients who cannot tolerate other antidepressants

Potential Disadvantages

- Patients with adequate folate levels

Primary Target Symptoms

- Depressed mood
- Cognitive symptoms



Pearls

- Numerous studies suggest that low plasma, red blood cell, and/or CSF levels of folate may be associated with depression in some patients
- Treatment with L-methylfolate seems to be safe, has few if any side effects, and is generally less expensive than augmenting

with a second branded antidepressant or atypical antipsychotic

- L-methylfolate is able to cross the blood-brain barrier and support the synthesis of monoamines
- Early studies suggest that those with obesity may be better responders
- Early studies suggest that those with genetic polymorphisms reducing the formation of L-methylfolate may be better responders



Suggested Reading

Bottiglieri T. Homocysteine and folate metabolism in depression. *Prog Neuropsychopharmacology Biol Psychiatry* 2005;29:1103–12.

Fava M, Mischoulon D. Folate in depression: efficacy, safety, differences in formulations, and clinical issues. *J Clin Psychiatry* 2009;70 (Suppl 5):S12–17.

Miller AL. The methylation, neurotransmitter, and antioxidant connections between folate and depression. *Altern Med Rev* 2008;13(3):216–26.

Stahl SM. L-methylfolate: A vitamin for your monoamines. *J Clin Psychiatry* 2008;69(9):1352–3.

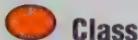
THERAPEUTICS

Brands

- Focalin
- Focalin XR

see index for additional brand names

Generic? Yes



Class

- Neuroscience-based Nomenclature: dopamine, norepinephrine reuptake inhibitor and releaser (DN-RIRe)
- Stimulant

Commonly Prescribed for

(bold for FDA approved)

- **Attention deficit hyperactivity disorder (ADHD) in children ages 6–17 (Focalin, Focalin XR) and in adults (Focalin XR)**
- Narcolepsy
- Treatment-resistant depression



How the Drug Works

- Increases norepinephrine and especially dopamine actions by blocking their reuptake
- Enhancement of dopamine and norepinephrine actions in certain brain regions (e.g., dorsolateral prefrontal cortex) may improve attention, concentration, executive function, and wakefulness
- Enhancement of dopamine actions in other brain regions (e.g., basal ganglia) may improve hyperactivity
- Enhancement of dopamine and norepinephrine in yet other brain regions (e.g., medial prefrontal cortex, hypothalamus) may improve depression, fatigue, and sleepiness

How Long Until It Works

- Onset of action can occur 30 minutes post-administration
- Can take several weeks to attain maximum therapeutic benefit

If It Works (for ADHD)

- The goal of treatment of ADHD is reduction of symptoms of inattentiveness, motor hyperactivity, and/or impulsiveness that disrupt social, school, and/or occupational functioning
- Continue treatment until all symptoms are under control or improvement is stable and then continue treatment indefinitely as long as improvement persists

- Reevaluate the need for treatment periodically
- Treatment for ADHD begun in childhood may need to be continued into adolescence and adulthood if continued benefit is documented

If It Doesn't Work (for ADHD)

- Consider adjusting dose or switching to a formulation of d,l-methylphenidate or to another agent
- Consider behavioral therapy
- Consider the presence of noncompliance and counsel patient and parents
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., bipolar disorder, substance abuse, medical illness, etc.)

★ Some ADHD patients and some depressed patients may experience lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require either augmenting with a mood stabilizer or switching to a mood stabilizer



Best Augmenting Combos for Partial Response or Treatment Resistance

- Best to attempt other monotherapies prior to augmenting
- For the expert, can combine immediate-release formulation of d-methylphenidate with a sustained-release formulation of d-methylphenidate for ADHD
- For the expert, can combine with modafinil or atomoxetine for ADHD
- For the expert, can occasionally combine with atypical antipsychotics in highly treatment-resistant cases of bipolar disorder or ADHD
- For the expert, can combine with antidepressants to boost antidepressant efficacy in highly treatment-resistant cases of depression while carefully monitoring patient

Tests

- Before treatment, assess for presence of cardiac disease (history, family history, physical exam)
- Blood pressure should be monitored regularly
- In children, monitor weight and height
- Periodic complete blood cell and platelet counts may be considered during prolonged therapy (rare leukopenia and/or anemia)

SIDE EFFECTS

How Drug Causes Side Effects

- Increases in norepinephrine peripherally can cause autonomic side effects, including tremor, tachycardia, hypertension, and cardiac arrhythmias
- Increases in norepinephrine and dopamine centrally can cause CNS side effects such as insomnia, agitation, psychosis, and substance abuse

Notable Side Effects

- * Insomnia, headache, exacerbation of tics, nervousness, irritability, overstimulation, tremor, dizziness
- Anorexia, nausea, abdominal pain, weight loss
- Can temporarily slow normal growth in children (controversial)
- Blurred vision



Life-Threatening or Dangerous Side Effects

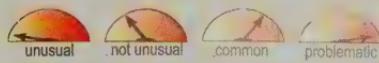
- Psychotic episodes, especially with parenteral abuse
- * Rare priapism
- Seizures
- Palpitations, tachycardia, hypertension
- Rare neuroleptic malignant syndrome
- Rare activation of hypomania, mania, or suicidal ideation (controversial)
- Cardiovascular adverse effects, sudden death in patients with preexisting cardiac structural abnormalities

Weight Gain



- Reported but not expected
- Some patients may experience weight loss

Sedation



- Reported but not expected
- Activation much more common than sedation

What to Do About Side Effects

- Wait
- Adjust dose
- Switch to a formulation of d,l-methylphenidate
- Switch to another agent

- For insomnia, avoid dosing in afternoon/evening

Best Augmenting Agents for Side Effects

- Beta blockers for peripheral autonomic side effects
- Dose reduction or switching to another agent may be more effective since most side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 2.5–10 mg twice per day

Dosage Forms

- Immediate-release tablet 2.5 mg, 5 mg, 10 mg
- Extended-release capsule 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg

How to Dose

- Immediate-release: for patients who are not taking racemic d,l-methylphenidate, initial 2.5 mg twice per day in 4-hour intervals; may adjust dose in weekly intervals by 2.5–5 mg/day; maximum dose generally 10 mg twice per day
- Immediate-release: for patients currently taking racemic d,l-methylphenidate, initial dose should be half the current dose of racemic d,l-methylphenidate; maximum dose generally 10 mg twice per day
- Extended-release: for children, same titration schedule as immediate-release but dosed once in the morning; maximum dose 30 mg/day
- Extended-release: for adults not taking racemic d,l-methylphenidate, initial 10 mg/day in the morning; may adjust dose in weekly intervals by 10 mg/day; maximum dose generally 40 mg/day



Dosing Tips

- * Immediate-release d-methylphenidate has the same onset of action and duration of action as immediate-release racemic d,l-methylphenidate (i.e., 2–4 hours) but at half the dose

- Extended-release d-methylphenidate contains half the dose as immediate-release beads and half as delayed-release beads, so the dose is released in 2 pulses
- Although d-methylphenidate is generally considered to be twice as potent as racemic d,l-methylphenidate, some studies suggest that the d-isomer is actually more than twice as effective as racemic d,l-methylphenidate
- Side effects are generally dose-related
- Off-label uses are dosed the same as for ADHD
- May be possible to dose only during the school week for some ADHD patients
- May be able to give drug holidays over the summer in order to reassess therapeutic utility and effects on growth and to allow catch-up from any growth suppression as well as to assess any other side effects and the need to reinstitute stimulant treatment for the next school term
- Avoid dosing late in the day because of the risk of insomnia
- Taking with food may delay peak actions for 2–3 hours

Overdose

- Vomiting, tremor, coma, convulsion, hyperreflexia, euphoria, confusion, hallucination, tachycardia, flushing, palpitations, sweating, hyperpyrexia, hypertension, arrhythmia, mydriasis, agitation, delirium, headache

Long-Term Use

- Often used long-term for ADHD when ongoing monitoring documents continued efficacy
- Dependence and/or abuse may develop
- Tolerance to therapeutic effects may develop in some patients
- Long-term stimulant use may be associated with growth suppression in children (controversial)
- Periodic monitoring of weight, blood pressure, CBC, platelet counts, and liver function may be prudent

Habit Forming

- High abuse potential, Schedule II drug
- Patients may develop tolerance, psychological dependence

How to Stop

- Taper to avoid withdrawal effects
- Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder and may require follow-up and reinstatement of treatment
- Careful supervision is required during withdrawal from abusive use since severe depression may occur

Pharmacokinetics

- d-threo-enantiomer of racemic d,l-methylphenidate
- Mean plasma elimination half-life approximately 2.2 hours (same as d,l-methylphenidate)
- Does not inhibit CYP450 enzymes



Drug Interactions

- May affect blood pressure and should be used cautiously with agents used to control blood pressure
- May inhibit metabolism of SSRIs, anticonvulsants (phenobarbital, phenytoin, primidone), TCAs, and coumarin anticoagulants, requiring downward dosage adjustments of these drugs
- Serious adverse effects may occur if combined with clonidine (controversial)
- Use with MAOIs, including within 14 days of MAOI use, is not advised, but this can sometimes be considered by experts who monitor depressed patients closely when other treatment options for depression fail
- CNS and cardiovascular actions of d-methylphenidate could theoretically be enhanced by combination with agents that block norepinephrine reuptake, such as the TCAs desipramine or protriptyline, venlafaxine, duloxetine, atomoxetine, milnacipran, and reboxetine
- Theoretically, antipsychotics should inhibit the stimulatory effects of d-methylphenidate
- Theoretically, d-methylphenidate could inhibit the antipsychotic actions of antipsychotics
- Theoretically, d-methylphenidate could inhibit the mood-stabilizing actions of atypical antipsychotics in some patients
- Combinations of d-methylphenidate with mood stabilizers (lithium, anticonvulsants,

atypical antipsychotics) is generally something for experts only, when monitoring patients closely and when other options fail

- Antacids or acid suppressants could alter the release of extended-release formulation



Other Warnings/ Precautions

- Use with caution in patients with any degree of hypertension, hyperthyroidism, or history of drug abuse
- Children who are not growing or gaining weight should stop treatment, at least temporarily
- May worsen motor and phonic tics
- May worsen symptoms of thought disorder and behavioral disturbance in psychotic patients
- Stimulants have a high potential for abuse and must be used with caution in anyone with a current or past history of substance abuse or alcoholism or in emotionally unstable patients
- Administration of stimulants for prolonged periods of time should be avoided whenever possible or done only with close monitoring, as it may lead to marked tolerance and drug dependence, including psychological dependence with varying degrees of abnormal behavior
- Particular attention should be paid to the possibility of subjects obtaining stimulants for nontherapeutic use or distribution to others and the drugs should in general be prescribed sparingly with documentation of appropriate use
- Usual dosing has been associated with sudden death in children with structural cardiac abnormalities
- Not an appropriate first-line treatment for depression or for normal fatigue
- May lower the seizure threshold
- Emergence or worsening of activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of a mood stabilizer and/or discontinuation of d-methylphenidate

Do Not Use

- If patient has extreme anxiety or agitation

- If patient has motor tics or Tourette's syndrome or if there is a family history of Tourette's, unless administered by an expert in cases when the potential benefits for ADHD outweigh the risks of worsening tics
- Should generally not be administered with an MAOI, including within 14 days of MAOI use, except in heroic circumstances and by an expert
- If patient has glaucoma
- If patient has structural cardiac abnormalities
- If patient has angioedema or anaphylaxis
- If there is a proven allergy to methylphenidate

SPECIAL POPULATIONS

Renal Impairment

- No dose adjustment necessary

Hepatic Impairment

- No dose adjustment necessary

Cardiac Impairment

- Use with caution, particularly in patients with recent myocardial infarction or other conditions that could be negatively affected by increased blood pressure
- Do not use in patients with structural cardiac abnormalities

Elderly

- Some patients may tolerate lower doses better



Children and Adolescents

- Safety and efficacy not established in children under age 6
- Use in young children should be reserved for the expert
- Methylphenidate has acute effects on growth hormone; long-term effects are unknown but weight and height should be monitored during long-term treatment
- Sudden death in children and adolescents with serious heart problems has been reported
- American Heart Association recommends EKG prior to initiating stimulant treatment in children, although not all experts agree



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Infants whose mothers took methylphenidate during pregnancy may experience withdrawal symptoms
- Racemic methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day throughout organogenesis
- Use in women of childbearing potential requires weighing potential benefits to the mother against potential risks to the fetus
- For ADHD patients, methylphenidate should generally be discontinued before anticipated pregnancies

Breast Feeding

- Unknown if methylphenidate is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- Recommended either to discontinue drug or bottle feed
- If infant shows signs of irritability, drug may need to be discontinued

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- The active d enantiomer of methylphenidate may be slightly more than twice as efficacious as racemic d,l-methylphenidate

Potential Disadvantages

- Patients with current or past substance abuse, bipolar disorder, or psychosis

Primary Target Symptoms

- Concentration, attention span
- Motor hyperactivity

- Impulsiveness
- Physical and mental fatigue
- Daytime sleepiness
- Depression



Pearls

- May be useful for treatment of depressive symptoms in medically ill elderly patients
- May be useful for treatment of post-stroke depression
- A classical augmentation strategy for treatment-refractory depression
- Specifically, may be useful for treatment of cognitive dysfunction and fatigue as residual symptoms of major depressive disorder unresponsive to multiple prior treatments
- May also be useful for the treatment of cognitive impairment, depressive symptoms, and severe fatigue in patients with HIV infection and in cancer patients
- Can be used to potentiate opioid analgesia and reduce sedation, particularly in end-of-life management
- Atypical antipsychotics may be useful in treating stimulant or psychotic consequences of overdose
- Some patients respond to or tolerate methylphenidate better than amphetamine, and vice versa
- Taking with food may delay peak actions of immediate-release d-methylphenidate for 2–3 hours
- Half-life and duration of clinical action tend to be shorter in younger children
- Drug abuse may actually be lower in ADHD adolescents treated with stimulants than in ADHD adolescents who are not treated
- New extended-release formulation is truly a once daily dose
- Extended-release capsule can be sprinkled over applesauce for patients unable to swallow the capsule
- Some patients may benefit from an occasional addition of an immediate-release dose of d-methylphenidate to the daily base dose of extended-release d-methylphenidate



Suggested Reading

Dexmethylphenidate – Novartis/Celgene.
Focalin, D-MPH, D-methylphenidate
hydrochloride, D-methylphenidate,
dexmethylphenidate, dexmethylphenidate
hydrochloride. Drugs R D 2002;3(4):279–82.

Keating GM, Figgitt DP. Dexmethylphenidate.
Drugs 2002;62(13):1899–904.

METHYLPHENIDATE (D,L)

THERAPEUTICS

- Brands • Concerta
- Metadate CD
- Ritalin
- Ritalin LA
- Methylin
- QuilliChew ER
- Quillivant XR
- Aptensio XR
- Daytrana

see index for additional brand names

Generic? Yes

Class

- Neuroscience-based Nomenclature: dopamine, norepinephrine reuptake inhibitor and releaser (DN-RIRe)
- Stimulant

Commonly Prescribed for

(bold for FDA approved)

- **Attention deficit hyperactivity disorder (ADHD) in children and adults (approved ages vary based on formulation)**
- **Narcolepsy (Metadate ER, Methylin ER, Ritalin, Ritalin SR)**
- Treatment-resistant depression



How the Drug Works

- Increases norepinephrine and especially dopamine actions by blocking their reuptake
- Enhancement of dopamine and norepinephrine actions in certain brain regions (e.g., dorsolateral prefrontal cortex) may improve attention, concentration, executive function, and wakefulness
- Enhancement of dopamine actions in other brain regions (e.g., basal ganglia) may improve hyperactivity
- Enhancement of dopamine and norepinephrine in yet other brain regions (e.g., medial prefrontal cortex, hypothalamus) may improve depression, fatigue, and sleepiness

How Long Until It Works

- Some immediate effects can be seen with first dosing
- Can take several weeks to attain maximum therapeutic benefit

If It Works (for ADHD)

- The goal of treatment of ADHD is reduction of symptoms of inattentiveness, motor hyperactivity, and/or impulsiveness that disrupt social, school, and/or occupational functioning
- Continue treatment until all symptoms are under control or improvement is stable and then continue treatment indefinitely as long as improvement persists
- Reevaluate the need for treatment periodically
- Treatment for ADHD begun in childhood may need to be continued into adolescence and adulthood if continued benefit is documented

If It Doesn't Work (for ADHD)

- Consider adjusting dose or switching to another formulation of d,l-methylphenidate or to another agent
- Consider behavioral therapy
- Consider the presence of noncompliance and counsel patient and parents
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., bipolar disorder, substance abuse, medical illness, etc.)

* Some ADHD patients and some depressed patients may experience lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require either augmenting with a mood stabilizer or switching to a mood stabilizer



Best Augmenting Combos for Partial Response or Treatment Resistance

- Best to attempt other monotherapies prior to augmenting
- For the expert, can combine immediate-release formulation with a sustained-release formulation of d,l-methylphenidate for ADHD
- For the expert, can combine with modafinil or atomoxetine for ADHD
- For the expert, can occasionally combine with atypical antipsychotics in highly treatment-resistant cases of bipolar disorder or ADHD
- For the expert, can combine with antidepressants to boost antidepressant efficacy in highly treatment-resistant cases of depression while carefully monitoring patient

METHYLPHENIDATE (D,L) (continued)

Tests

- Before treatment, assess for presence of cardiac disease (history, family history, physical exam)
- Blood pressure should be monitored regularly
- In children, monitor weight and height
- Periodic complete blood cell and platelet counts may be considered during prolonged therapy (rare leukopenia and/or anemia)

SIDE EFFECTS

How Drug Causes Side Effects

- Increases in norepinephrine peripherally can cause autonomic side effects, including tremor, tachycardia, hypertension, and cardiac arrhythmias
- Increases in norepinephrine and dopamine centrally can cause CNS side effects such as insomnia, agitation, psychosis, and substance abuse

Notable Side Effects

- ✿ Insomnia, headache, exacerbation of tics, nervousness, irritability, overstimulation, tremor, dizziness
- Anorexia, nausea, abdominal pain, weight loss
- Can temporarily slow normal growth in children (controversial)
- Blurred vision
- Transdermal: application site reactions, including contact sensitization (erythema, edema, papules, vesicles) and chemical leukoderma



Life-Threatening or Dangerous Side Effects

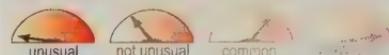
- ✿ Rare priapism
- Psychotic episodes, especially with parenteral abuse
- Seizures
- Palpitations, tachycardia, hypertension
- Rare neuroleptic malignant syndrome
- Rare activation of hypomania, mania, or suicidal ideation (controversial)
- Cardiovascular adverse effects, sudden death in patients with preexisting cardiac structural abnormalities

Weight Gain



- Reported but not expected
- Some patients may experience weight loss

Sedation



- Reported but not expected
- Activation much more common than sedation

What to Do About Side Effects

- Wait
- Adjust dose
- Switch to another formulation of d,l-methylphenidate
- Switch to another agent
- For insomnia, avoid dosing in afternoon/evening

Best Augmenting Agents for Side Effects

- Beta blockers for peripheral autonomic side effects
- Dose reduction or switching to another agent may be more effective since most side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- ADHD (oral): up to 2 mg/kg per day in children 6 years and older, with a maximum daily dose of 60 mg/day; in adults usually 20–30 mg/day, but may use up to 40–60 mg/day
- ADHD (transdermal): 10–30 mg/9 hours
- Narcolepsy: 20–60 mg/day in 2–3 divided doses

Dosage Forms

- Immediate-release tablets 5 mg, 10 mg, 20 mg (Ritalin, generic methylphenidate)
- Oral solution 5 mg/mL, 10 mg/5 mL (Methyltin)
- Older sustained-release tablets 10 mg, 20 mg (Methyltin ER); 20 mg (Ritalin SR, Metadate ER)
- ✿ Newer sustained-release capsules 10 mg, 20 mg, 30 mg, 40 mg, 60 mg (Ritalin LA);

10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg (Metadate CD)

* Newer sustained-release tablets 18 mg, 27 mg, 36 mg, 54 mg (Concerta)

- Sustained-release chewable tablets 20 mg scored, 30 mg, 40 mg (QuilliChew ER)
- Extended-release capsule, multi-layer release (Aptensio XR) 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg
- Extended-release oral suspension 5 mg/mL (Quillivant XR)
- Transdermal patch 27 mg/12.5 cm², (10 mg/9 hr; 1.1 mg/hr), 41.3 mg/18.75 cm² (15 mg/9 hr; 1.6 mg/hr), 55 mg/25 cm² (20 mg/9 hr; 2.2 mg/hr), 82.5 mg/37.5 cm² (30 mg/9 hr; 3.3 mg/hr)

How to Dose

- Immediate-release Ritalin, generic methylphenidate (2–4 hour duration of action)
 - ADHD: initial 5 mg in morning, 5 mg at lunch; can increase by 5–10 mg each week; maximum dose generally 60 mg/day
 - Narcolepsy: give each dose 30–45 minutes before meals; maximum dose generally 60 mg/day
- Older extended-release Ritalin SR, Methylin SR, and Metadate ER
 - These formulations have a duration of action of approximately 4–6 hours; therefore, these formulations may be used in place of immediate-release formulations when the 4–6 hour dosage of these sustained-release formulations corresponds to the titrated 4–6 hour dosage of the immediate-release formulation
 - Average dose is 20–30 mg/day, usually in 2 divided doses
- * Newer sustained-release formulations for ADHD
 - Concerta (up to 12 hours duration of action): initial 18 mg/day in morning; can increase by 18 mg each week; maximum dose generally 72 mg/day
 - Ritalin LA, Metadate CD, QuilliChew ER (up to 8 hours duration of action): initial 20 mg once daily; dosage may be adjusted in weekly increments of 10 mg or 20 mg (QuilliChew ER only) to a maximum of 60 mg/day taken in the morning

• Quillivant XR (up to 12-hour duration): initial 20 mg once daily; dosage may be adjusted in weekly increments of 10–20 mg to a maximum of 60 mg/day taken in the morning

• Aptensio XR (up to 12-hour duration): initial 10 mg once daily; dosage may be adjusted in weekly increments of 10 mg to a maximum of 60 mg/day taken in the morning

• * Transdermal formulation for ADHD

- Initial 10 mg/9 hours; can increase by 5 mg/9 hours every week; maximum dose generally 30 mg/9 hours
- Patch should be applied 2 hours before effect is needed and should be worn for 9 hours
- Patients should follow the same titration schedule when they are naive to methylphenidate or are switching from another formulation



Dosing Tips

- Clinical duration of action often differs from pharmacokinetic half-life
- Taking oral formulations with food may delay peak actions for 2–3 hours
- * Immediate-release formulations (Ritalin, Methylin, generic methylphenidate) have 2–4 hour durations of clinical action
- * Older sustained-release formulations such as Methylin ER, Ritalin SR, Metadate ER, and generic methylphenidate sustained-release all have approximately 4–6 hour durations of clinical action, which for most patients is generally not long enough for once daily dosing in the morning and thus generally requires lunchtime dosing at school
- * The newer sustained-release Metadate CD has an early peak and an 8-hour duration of action
- * The newer sustained-release Ritalin LA also has an early peak and an 8-hour duration of action, with 2 pulses (immediate and after 4 hours)
- * The newer sustained-release Concerta trilayer tablet has longest duration of action (12 hours)
- Most sustained-release formulations (especially Concerta, Metadate CD, and Ritalin LA) should not be chewed but rather should only be swallowed whole

- QuilliChew ER is a chewable tablet and can be taken with or without food
- Newer sustained-release formulations have a sufficiently long duration of clinical action to eliminate the need for a lunchtime dosing if taken in the morning
- This innovation can be an important practical element in stimulant utilization, eliminating the hassle and pragmatic difficulties of lunchtime dosing at school, including storage problems, potential diversion, and the need for a medical professional to supervise dosing away from home
- Off-label uses are dosed the same as for ADHD
- May be possible to dose only during the school week for some ADHD patients
- May be able to give drug holidays over the summer in order to reassess therapeutic utility and effects on growth and to allow catch-up from any growth suppression as well as to assess any other side effects and the need to reinstitute stimulant treatment for the next school term
- Avoid dosing late in the day because of the risk of insomnia
- Concerta tablet does not change shape in the gastrointestinal tract and generally should not be used in patients with gastrointestinal narrowing because of the risk of intestinal obstruction
- Side effects are generally dose-related
- Transdermal patch should be applied to dry, intact skin on the hip
- New application site should be selected for each day; only one patch should be applied at a time; patches should not be cut
- Avoid touching the exposed (sticky) side of the patch, and after application, wash hands with soap and water; do not touch eyes until after hands have been washed
- Heat can increase the amount of methylphenidate absorbed from the transdermal patch, so patients should avoid exposing the application site to external source of direct heat (e.g., heating pads, prolonged direct sunlight)
- If a patch comes off a new patch may be applied at a different site; total daily wear time should remain 9 hours regardless of number of patches used
- Early removal of transdermal patch can be useful to terminate drug action when desired

Overdose

- Vomiting, tremor, coma, convulsion, hyperreflexia, euphoria, confusion, hallucination, tachycardia, flushing, palpitations, sweating, hyperprexia, hypertension, arrhythmia, mydriasis

Long-Term Use

- Often used long-term for ADHD when ongoing monitoring documents continued efficacy
- Dependence and/or abuse may develop
- Tolerance to therapeutic effects may develop in some patients
- Long-term stimulant use may be associated with growth suppression in children (controversial)
- Periodic monitoring of weight, blood pressure, CBC, platelet counts, and liver function may be prudent

Habit Forming

- High abuse potential, Schedule II drug
- Patients may develop tolerance, psychological dependence

How to Stop

- Taper to avoid withdrawal effects
- Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder and may require follow-up and reinstitution of treatment
- Careful supervision is required during withdrawal from abusive use since severe depression may occur

Pharmacokinetics

- Average half-life in adults is 3.5 hours (1.3–7.7 hours)
- Average half-life in children is 2.5 hours (1.5–5 hours)
- First-pass metabolism is not extensive with transdermal dosing, thus resulting in notably higher exposure to methylphenidate and lower exposure to metabolites as compared to oral dosing



Drug Interactions

- May affect blood pressure and should be used cautiously with agents used to control blood pressure
- May inhibit metabolism of SSRIs, anticonvulsants (phenobarbital, phenytoin, primidone), TCAs, and coumarin

anticoagulants, requiring downward dosage adjustments of these drugs

- Serious adverse effects may occur if combined with clonidine (controversial)
- Use with MAOIs, including within 14 days of MAOI use, is not advised, but this can sometimes be considered by experts who monitor depressed patients closely when other treatment options for depression fail
- CNS and cardiovascular actions of d,l-methylphenidate could theoretically be enhanced by combination with agents that block norepinephrine reuptake, such as the TCAs desipramine or protriptyline, venlafaxine, duloxetine, atomoxetine, milnacipran, and reboxetine
- Theoretically, antipsychotics should inhibit the stimulatory effects of d,l-methylphenidate
- Theoretically, d,l-methylphenidate could inhibit the antipsychotic actions of antipsychotics
- Theoretically, d,l-methylphenidate could inhibit the mood-stabilizing actions of atypical antipsychotics in some patients
- Combination of d,l-methylphenidate with mood stabilizers (lithium, anticonvulsants, atypical antipsychotics) is generally something for experts only, when monitoring patients closely and when other options fail



Other Warnings/ Precautions

- Use with caution in patients with any degree of hypertension, hyperthyroidism, or history of drug abuse
- Children who are not growing or gaining weight should stop treatment, at least temporarily
- May worsen motor and phonic tics
- May worsen symptoms of thought disorder and behavioral disturbance in psychotic patients
- Stimulants have a high potential for abuse and must be used with caution in anyone with a current or past history of substance abuse or alcoholism or in emotionally unstable patients
- Administration of stimulants for prolonged periods of time should be avoided whenever possible or done only with close monitoring, as it may lead to marked

tolerance and drug dependence, including psychological dependence with varying degrees of abnormal behavior

- Particular attention should be paid to the possibility of subjects obtaining stimulants for nontherapeutic use or distribution to others and the drugs should in general be prescribed sparingly with documentation of appropriate use
- Usual dosing has been associated with sudden death in children with structural cardiac abnormalities
- Not an appropriate first-line treatment for depression or for normal fatigue
- May lower the seizure threshold
- Emergence or worsening of activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of a mood stabilizer and/or discontinuation of d,l-methylphenidate
- Permanent skin color loss, known as chemical leukoderma, may occur with use of the transdermal Daytrana patch; patients should be advised to watch for signs of skin color changes and if they occur alternative treatment options should be considered
- Certain transdermal patches containing even small traces of aluminum or other metals in the adhesive backing can cause skin burns if worn during MRI, so warn patients taking the transdermal formulation about this possibility and advise them to disclose this information if they need an MRI

Do Not Use

- If patient has extreme anxiety or agitation
- If patient has motor tics or Tourette's syndrome or if there is a family history of Tourette's, unless administered by an expert in cases when the potential benefits for ADHD outweigh the risks of worsening tics
- Should generally not be administered with an MAOI, including within 14 days of MAOI use, except in heroic circumstances and by an expert
- If patient has glaucoma
- If patient has structural cardiac abnormalities
- If there is a proven allergy to methylphenidate

SPECIAL POPULATIONS

Renal Impairment

- No dose adjustment necessary

Hepatic Impairment

- No dose adjustment necessary

Cardiac Impairment

- Use with caution, particularly in patients with recent myocardial infarction or other conditions that could be negatively affected by increased blood pressure
- Do not use in patients with structural cardiac abnormalities

Elderly

- Some patients may tolerate lower doses better



Children and Adolescents

- Safety and efficacy not established in children under age 6
- Use in young children should be reserved for the expert
- Methylphenidate has acute effects on growth hormone; long-term effects are unknown but weight and height should be monitored during long-term treatment
- Sudden death in children and adolescents with serious heart problems has been reported
- American Heart Association recommends EKG prior to initiating stimulant treatment in children, although not all experts agree



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLRL or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Infants whose mothers took methylphenidate during pregnancy may experience withdrawal symptoms

- Racemic methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day throughout organogenesis
 - Use in women of childbearing potential requires weighing potential benefits to the mother against potential risks to the fetus
- ✳ For ADHD patients, methylphenidate should generally be discontinued before anticipated pregnancies

Breast Feeding

- Unknown if methylphenidate is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- ✳ Recommended either to discontinue drug or bottle feed
- If infant shows signs of irritability, drug may need to be discontinued

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Established long-term efficacy as a first-line treatment for ADHD
- Multiple options for drug delivery, peak actions, and duration of action

Potential Disadvantages

- Patients with current or past substance abuse
- Patients with current or past bipolar disorder or psychosis

Primary Target Symptoms

- Concentration, attention span
- Motor hyperactivity
- Impulsiveness
- Physical and mental fatigue
- Daytime sleepiness
- Depression



Pearls

- ✳ May be useful for treatment of depressive symptoms in medically ill elderly patients
- ✳ May be useful for treatment of post-stroke depression
- ✳ A classical augmentation strategy for treatment-refractory depression
- ✳ Specifically, may be useful for treatment of cognitive dysfunction and fatigue as residual symptoms of major depressive

disorder unresponsive to multiple prior treatments

- ✿ May also be useful for the treatment of cognitive impairment, depressive symptoms, and severe fatigue in patients with HIV infection and in cancer patients
- Can be used to potentiate opioid analgesia and reduce sedation, particularly in end-of-life management
- Atypical antipsychotics may be useful in treating stimulant or psychotic consequences of overdose
- Some patients respond to or tolerate methylphenidate better than amphetamine and vice versa
- Taking with food may delay peak actions of oral formulations for 2–3 hours
- Half-life and duration of clinical action tend to be shorter in younger children
- Drug abuse may actually be lower in ADHD adolescents treated with stimulants than in ADHD adolescents who are not treated
- Older sustained-release technologies for methylphenidate were not significant advances over immediate-release methylphenidate because they did not eliminate the need for lunchtime dosing or allow once daily administration
- ✿ Newer sustained-release technologies are truly once a day dosing systems
- ✿ Metadate CD and Ritalin LA are somewhat similar to each other, both with an early peak and duration of action of about 8 hours
- ✿ Concerta has less of an early peak but a longer duration of action (up to 12 hours)

✿ Concerta trilayer tablet consists of 3 compartments (2 containing drug, 1 a “push” compartment) and an orifice at the head of the first drug compartment; water fills the push compartment and gradually pushes drug up and out of the tablet through the orifice

✿ Concerta may be preferable for those ADHD patients who work in the evening or do homework up to 12 hours after morning dosing

✿ Metadate CD and Ritalin LA may be preferable for those ADHD patients who lose their appetite for dinner or have insomnia with Concerta

- Some patients may benefit from an occasional addition of 5–10 mg of immediate-release methylphenidate to their daily base of sustained-release methylphenidate
- Transdermal formulation may confer lower abuse potential than oral formulations
- Transdermal formulation may enhance adherence to treatment compared to some oral formulations because it allows once daily application with all day efficacy, has a smoother absorption curve, and allows for daily customization of treatment (i.e., it can be removed early if desired)
- On the other hand, transdermal formulation has slower onset than oral formulations, requires a specific removal time, can cause skin sensitization, can be large depending on dose, and may lead to reduced efficacy if removed prematurely



Suggested Reading

Challman TD, Lipsky JJ. Methylphenidate: its pharmacology and uses. Mayo Clin Proc 2000;75:711–21.

Kimko HC, Cross JT, Abernethy DR. Pharmacokinetics and clinical effectiveness of methylphenidate. Clin Pharmacokinet 1999;37:457–70.

Wolraich ML, Greenhill LL, Pelham W, et al. Randomized, controlled trial of oros methylphenidate once a day in children with attention-deficit/hyperactivity disorder. Pediatrics 2001;108:883–92.

THERAPEUTICS

Brands • Lerivon

see index for additional brand names

Generic? Yes**Class**

- Neuroscience-based Nomenclature: norepinephrine multi-modal (N-MM)
- Tetracyclic antidepressant
- Noradrenergic agent

Commonly Prescribed for

(bold for FDA approved)

- Depression
- Anxiety
- Insomnia
- Treatment-resistant depression

**How the Drug Works**

- Blocks alpha 2 adrenergic presynaptic receptor, thereby increasing norepinephrine neurotransmission
- This is a novel mechanism independent of norepinephrine reuptake blockade
- Blocks alpha 2 adrenergic presynaptic receptors but also alpha 1 adrenergic receptors on serotonin neurons, thereby causing little increase in serotonin neurotransmission
- Blocks 5HT2A, 5HT2C, and 5HT3 serotonin receptors
- Blocks H1 histamine receptors

How Long Until It Works

- Actions on insomnia and anxiety can start shortly after initiation of dosing
- Onset of therapeutic actions in depression, however, is usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses

- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine is stopped
- Continue treatment until all symptoms are gone (remission)
- Once symptoms gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders may also need to be indefinite

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer

**Best Augmenting Combos for Partial Response or Treatment Resistance**

- SSRIs, SNRIs, bupropion, reboxetine, atomoxetine (use combinations of antidepressant with caution as this may activate bipolar disorder and suicidal ideation)
- Modafinil, especially for fatigue, sleepiness, and lack of concentration
- Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression, or treatment-resistant depression
- Benzodiazepines

Tests

- Baseline ECG is recommended for patients over age 50

- May need to monitor blood count during treatment for those with blood dyscrasias, leucopenia, or granulocytopenia
- Since some antidepressants such as mianserin can be associated with weight gain, before starting treatment, weigh all patients and determine if the patient is already overweight (BMI 25.0–29.9) or obese (BMI ≥30)
- Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–125 mg/dL), diabetes (fasting plasma glucose >126 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management
- ✿ Monitor weight and BMI during treatment
- ✿ While giving a drug to a patient who has gained >5% of initial weight, consider evaluating for the presence of pre-diabetes, diabetes, or dyslipidemia, or consider switching to a different antidepressant

SIDE EFFECTS

How Drug Causes Side Effects

- Most side effects are immediate but often go away with time
- ✿ Histamine 1 receptor antagonism may explain sedative effects
- ✿ Histamine 1 receptor antagonism plus 5HT2C antagonism may explain some aspects of weight gain

Notable Side Effects

- Sedation
- Increased appetite, weight gain



Life-Threatening or Dangerous Side Effects

- Rare seizures
- Rare blood dyscrasias
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Many experience and/or can be significant in amount

Sedation



- Many experience and/or can be significant in amount
- Generally transient

What to Do About Side Effects

- Wait
- Wait
- Wait
- Switch to another drug

Best Augmenting Agents for Side Effects

- Often best to try another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
- Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Many side effects cannot be improved with an augmenting agent
- Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of mianserin

DOSING AND USE

Usual Dosage Range

- 30–60 mg/day

Dosage Forms

- Tablet 10 mg, 30 mg, 60 mg

How to Dose

- Initial 30 mg/day; maximum usually 90 mg/day



Dosing Tips

- Can be dosed once or twice daily
- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar disorder and switch to a mood stabilizer or an atypical antipsychotic

Overdose

- Relatively safe in overdose; sedation, hypertension, or hypotension

Long-Term Use

- Safe

Habit Forming

- Not expected

How to Stop

- Taper is prudent to avoid withdrawal effects, but tolerance, dependence, and withdrawal effects not reliably reported

Pharmacokinetics

- Half-life 12–29 hours



Drug Interactions

- Tramadol increases the risk of seizures in patients taking an antidepressant
- Carbamazepine and phenytoin may reduce mianserin levels
- Theoretically could cause a fatal “serotonin syndrome” when combined with MAOIs, so do not use with MAOIs or for at least 14 days after MAOIs are stopped unless you are an expert and only for treatment-resistant cases that may justify the risk
- Do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing mianserin



Other Warnings/ Precautions

- Drug may lower white blood cell count (rare; may not be increased compared to other antidepressants but controlled studies lacking)
- Avoid alcohol, which may increase sedation and cognitive and motor effects

- Use with caution in patients with history of seizures
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is taking an MAOI
- If there is a proven allergy to mianserin

SPECIAL POPULATIONS

Renal Impairment

- Dose adjustment not necessary

Hepatic Impairment

- Dose adjustment not necessary

Cardiac Impairment

- Baseline ECG is recommended
- Drug should be used with caution

Elderly

- Baseline ECG is recommended for patients over age 50
- Some patients may tolerate lower doses better
- Blood dyscrasias, though still rare, may be more common in the elderly



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment

- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Safety and efficacy have not been established



Pregnancy

- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy

Breast Feeding

- Some drug is found in mother's breast milk
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients, this may mean continuing treatment during breast feeding

Potential Advantages

- Patients particularly concerned about sexual side effects
- Patients with symptoms of anxiety
- As an augmenting agent to boost the efficacy of other antidepressants
- Patients with cardiovascular disease

Potential Disadvantages

- Patients particularly concerned about gaining weight
- Patients with low energy

Primary Target Symptoms

- Depressed mood
- Sleep disturbance
- Anxiety



Pearls

- ✿ Adding alpha 2 antagonism to agents that block serotonin and/or norepinephrine reuptake may be synergistic for severe depression
- Adding mianserin to venlafaxine or SSRIs may reverse drug-induced anxiety and insomnia
- Efficacy of mianserin for depression in cancer patients has been shown in small controlled studies
- ✿ Only causes sexual dysfunction infrequently
- Generally better tolerated than TCAs, including safer in overdose
- General lack of cardiovascular toxicity



Suggested Reading

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De Ridder JJ. Mianserin: result of a decade of antidepressant research. *Pharm Weekbl Sci* 1982;4(5):139-45.

Leinonen E, Koponen H, Lepola U. Serum mianserin and ageing. *Prog Neuropsychopharmacol Biol Psychiatry* 1994;18(5):833-45.

Rotzinger S, Bourin M, Akimoto Y, Coutts RT, Baker GB. Metabolism of some "second-" and "fourth-" generation antidepressants: iprindole, viloxazine, bupropion, mianserin, maprotiline, trazodone, nefazodone, and venlafaxine. *Cell Mol Neurobiol* 1999;19(4):427-42.

Wakeling A. Efficacy and side effects of mianserin, a tetracyclic antidepressant. *Postgrad Med J* 1983;59(690):229-31.

THERAPEUTICS

- Brands**
- Toledomin
 - Ixel
 - Savella

see index for additional brand names

Generic? No



Class

- Neuroscience-based Nomenclature: serotonin, norepinephrine reuptake inhibitor (SN-Ri)
- SNRI (dual serotonin and norepinephrine reuptake inhibitor); antidepressant; chronic pain treatment

Commonly Prescribed for

(bold for FDA approved)

- **Fibromyalgia**
- Major depressive disorder
- Neuropathic pain/chronic pain



How the Drug Works

- Boosts neurotransmitters serotonin, norepinephrine/noradrenaline, and dopamine
- Blocks serotonin reuptake pump (serotonin transporter), presumably increasing serotonergic neurotransmission
- Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing noradrenergic neurotransmission
- Presumably desensitizes both serotonin 1A receptors and beta adrenergic receptors
- Weak noncompetitive NMDA-receptor antagonist (high doses), which may contribute to actions in chronic pain
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, milnacipran can increase dopamine neurotransmission in this part of the brain

How Long Until It Works

- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms in depression

If It Works

- The goal of treatment of depression is complete remission of current symptoms as well as prevention of future relapses
- The goal of treatment of fibromyalgia and chronic neuropathic pain is to reduce symptoms as much as possible, especially in combination with other treatments
- Treatment of depression most often reduces or even eliminates symptoms, but is not a cure since symptoms can recur after medicine stopped
- Treatment of fibromyalgia and chronic neuropathic pain may reduce symptoms, but rarely eliminates them completely, and is not a cure since symptoms can recur after medicine is stopped
- Continue treatment of depression until all symptoms are gone (remission)
- Once symptoms of depression are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in fibromyalgia and chronic neuropathic pain may also need to be indefinite, but long-term treatment is not well studied in these conditions

If It Doesn't Work

- Many depressed patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other depressed patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some depressed patients who have an initial response may relapse even though they continue treatment, sometimes called “poop-out”
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and switch to a mood stabilizer



Best Augmenting Combos for Partial Response or Treatment Resistance

- Augmentation experience is limited compared to other antidepressants
- Benzodiazepines can reduce insomnia and anxiety
- Adding other agents to milnacipran for treating depression could follow the same practice for augmenting SSRIs or other SNRIs if done by experts while monitoring carefully in difficult cases
- Although no controlled studies and little clinical experience, adding other agents for treating fibromyalgia and chronic neuropathic pain could theoretically include gabapentin, tiagabine, other anticonvulsants, or even opiates if done by experts while monitoring carefully in difficult cases
- Mirtazapine, bupropion, reboxetine, atomoxetine (use combinations of antidepressants with caution as this may activate bipolar disorder and suicidal ideation)
- Modafinil, especially for fatigue, sleepiness, and lack of concentration
- Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression, or treatment-resistant depression
- Hypnotics or trazodone for insomnia
- Classically, lithium, buspirone, or thyroid hormone

Tests

- Check blood pressure before initiating treatment and regularly during treatment

SIDE EFFECTS

How Drug Causes Side Effects

- Theoretically due to increases in serotonin and norepinephrine concentrations at receptors in parts of the brain and body other than those that cause therapeutic actions (e.g., unwanted actions of serotonin in sleep centers causing insomnia, unwanted actions of norepinephrine on acetylcholine release causing urinary retention or constipation)
- Most side effects are immediate but often go away with time

Notable Side Effects

- Most side effects increase with higher doses, at least transiently
- Headache, nervousness, insomnia, sedation
- Nausea, diarrhea, decreased appetite
- Sexual dysfunction (abnormal ejaculation/orgasm, impotence)
- Asthenia, sweating
- SIADH (syndrome of inappropriate antidiuretic hormone secretion)
- Dose-dependent increased blood pressure
- Dry mouth, constipation
- Dysuria, urological complaints, urinary hesitancy, urinary retention
- Increase in heart rate
- Palpitations



Life-Threatening or Dangerous Side Effects

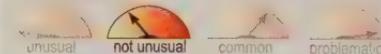
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)
- Rare seizures

Weight Gain



- Reported but not expected

Sedation



- Occurs in significant minority

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- In a few weeks, switch or add other drugs

Best Augmenting Agents for Side Effects

- For urinary hesitancy, give an alpha 1 blocker such as tamsulosin or naftopidil
- Often best to try another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
- Trazodone or a hypnotic for insomnia

- Bupropion, sildenafil, vardenafil, or tadalafil for sexual dysfunction
- Benzodiazepines for anxiety, agitation
- Mirtazapine for insomnia, agitation, and gastrointestinal side effects
- Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of milnacipran

DOSING AND USE

Usual Dosage Range

- 30–200 mg/day in 2 doses

Dosage Forms

- Capsule 25 mg, 50 mg (France, other European countries, and worldwide markets)
- Capsule 15 mg, 25 mg, 50 mg (Japan)
- Tablet 12.5 mg, 25 mg, 50 mg, 100 mg

How to Dose

- Should be administered in 2 divided doses
- Initial 12.5 mg once daily; increase to 25 mg/day in 2 divided doses on day 2; increase to 50 mg/day in 2 divided doses on day 4; increase to 100 mg/day in 2 divided doses on day 7; maximum dose generally 200 mg/day



Dosing Tips

- Preferred dose for fibromyalgia may be 100 mg twice daily
- Higher doses usually well tolerated in fibromyalgia patients
- Once daily dosing has far less consistent efficacy, so only give as twice daily
- Higher doses (>200 mg/day) not consistently effective in all studies of depression

- Nevertheless, some patients respond better to higher doses (200–300 mg/day) than to lower doses
- Different doses in different countries
- Different doses in different indications and different populations
- Preferred dose for depression may be 50 mg twice daily to 100 mg twice daily in France
- Preferred dose for depression in the elderly may be 15 mg twice daily to 25 mg twice daily in Japan
- Preferred dosing for depression in other adults may be 25 mg twice daily to 50 mg twice daily in Japan
- Thus, clinicians must be aware that titration of twice daily dosing across a 10-fold range (30 mg–300 mg total daily dose) can optimize milnacipran's efficacy in broad clinical use
- Patients with agitation or anxiety may require slower titration to optimize tolerability
- No pharmacokinetic drug interactions (not an inhibitor of CYP450 2D6 or 3A4)
- As milnacipran is a more potent norepinephrine reuptake inhibitor than a serotonin reuptake inhibitor, some patients may require dosing at the higher end of the dosing range to obtain robust dual SNRI actions
- At high doses, NMDA glutamate antagonist actions may be a factor

Overdose

- Vomiting, hypertension, sedation, tachycardia
- The emetic effect of high doses of milnacipran may reduce the risk of serious adverse effects

Long-Term Use

- Safe

Habit Forming

- No

How to Stop

- Taper is prudent, but usually not necessary

Pharmacokinetics

- Half-life 8 hours
- No active metabolite

SPECIAL POPULATIONS**Drug Interactions**

- Tramadol increases the risk of seizures in patients taking an antidepressant
- Can cause a fatal “serotonin syndrome” when combined with MAOIs, so do not use with MAOIs or for at least 14 days after MAOIs are stopped
- Do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing milnacipran
- Possible increased risk of bleeding, especially when combined with anticoagulants (e.g., warfarin, NSAIDs)
- Switching from or addition of other norepinephrine reuptake inhibitors should be done with caution, as the additive pro-noradrenergic effects may enhance therapeutic actions in depression, but also enhance noradrenergically mediated side effects
- Few known adverse pharmacokinetic drug interactions

**Other Warnings/
Precautions**

- Use with caution in patients with history of seizures
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- Can cause mild elevations in ALT/AST, so avoid use with alcohol or in cases of chronic liver disease
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient has uncontrolled angle-closure glaucoma
- If patient is taking an MAOI
- If there is a proven allergy to milnacipran

Renal Impairment

- Use caution for moderate impairment
- For severe impairment, 50 mg/day; can increase to 100 mg/day if needed
- Not recommended for patients with end-stage renal disease

Hepatic Impairment

- No dose adjustment necessary
- Not recommended for use in chronic liver disease

Cardiac Impairment

- Drug should be used with caution

Elderly

- Some patients may tolerate lower doses better
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older

**Children and Adolescents**

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Not well studied

**Pregnancy**

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001

- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester
- Nonetheless, continuous treatment during pregnancy may be necessary and has not been proven to be harmful to the fetus
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy
- Neonates exposed to SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding; reported symptoms are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome, and include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying

Breast Feeding

- Some drug is found in mother's breast milk
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients, this may mean continuing treatment during breast feeding

- Patients with atypical depression
- Patients with depression may have higher remission rates on SNRIs than on SSRIs
- Depressed patients with somatic symptoms, fatigue, and pain

Potential Disadvantages

- Patients with urologic disorders, prostate disorders
- Patients with borderline or uncontrolled hypertension
- Patients with agitation and anxiety (short-term)

Primary Target Symptoms

- Pain
- Physical symptoms
- Depressed mood
- Energy, motivation, and interest
- Sleep disturbance



Pearls

- Approved in the USA. for use in pain and fibromyalgia
- Not studied in stress urinary incontinence
- Not well studied in ADHD or anxiety disorders, but may be effective
- Has greater potency for norepinephrine reuptake blockade than for serotonin reuptake blockade, but this is of unclear clinical significance as a differentiating feature from other SNRIs, although it might contribute to its therapeutic activity in fibromyalgia and chronic pain
- Onset of action in fibromyalgia may be somewhat faster than depression (i.e., 2 weeks rather than 2–8 weeks)
- Therapeutic actions in fibromyalgia are partial, with symptom reduction but not necessarily remission of painful symptoms in many patients
- Potent noradrenergic actions may account for possibly higher incidence of sweating and urinary hesitancy than other SNRIs
- Urinary hesitancy more common in men than women and in older men than in younger men
- Alpha 1 antagonists such as tamsulosin or naftopidil can reverse urinary hesitancy or retention
- Alpha 1 antagonists given prophylactically may prevent urinary hesitancy or retention

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Fibromyalgia, chronic pain syndrome
- Patients with retarded depression
- Patients with hypersomnia

MILNACIPRAN (continued)

- in patients at higher risk, such as elderly men with borderline urine flow
- May be better tolerated than tricyclic or tetracyclic antidepressants in the treatment of fibromyalgia or other chronic pain syndromes
- No pharmacokinetic interactions or elevations in plasma drug levels of tricyclic or tetracyclic antidepressants when adding or switching to or from milnacipran



Suggested Reading

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Derry S, Gill D, Phillips T, Moore RA. Milnacipran for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* 2012;14(3):CD008244.

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THERAPEUTICS

Brands • Remeron*see index for additional brand names***Generic?** Yes**Class**

- Neuroscience-based Nomenclature: serotonin, norepinephrine receptor antagonist (SN-RAn)
- Alpha 2 antagonist; NaSSA (noradrenaline and specific serotonergic agent); dual serotonin and norepinephrine agent; antidepressant

Commonly Prescribed for*(bold for FDA approved)*

- **Major depressive disorder**
- Panic disorder
- Generalized anxiety disorder
- Posttraumatic stress disorder

**How the Drug Works**

- Boost neurotransmitters serotonin and norepinephrine/noradrenaline
- Blocks alpha 2 adrenergic presynaptic receptor, thereby increasing norepinephrine neurotransmission
- Blocks alpha 2 adrenergic presynaptic receptor on serotonin neurons (heteroreceptors), thereby increasing serotonin neurotransmission
- This is a novel mechanism independent of norepinephrine and serotonin reuptake blockade
- Blocks 5HT2A, 5HT2C, and 5HT3 serotonin receptors
- Blocks H1 histamine receptors

How Long Until It Works

- ✳ Actions on insomnia and anxiety can start shortly after initiation of dosing
- Onset of therapeutic actions in depression, however, is usually not immediate, but often delayed 2–4 weeks
 - If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all
 - May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Continue treatment until all symptoms are gone (remission)
- Once symptoms are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders may also need to be indefinite

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer

**Best Augmenting Combos for Partial Response or Treatment Resistance**

- SSRIs, bupropion, reboxetine, atomoxetine (use combinations of antidepressants with caution as this may activate bipolar disorder and suicidal ideation)
- ✳ Venlafaxine ("California rocket fuel"; a potentially powerful dual serotonin and norepinephrine combination, but observe for activation of bipolar disorder and suicidal ideation)
- Modafinil, especially for fatigue, sleepiness, and lack of concentration

- Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression or treatment-resistant depression
- Benzodiazepines
- Hypnotics or trazodone for insomnia

Tests

- None for healthy individuals
 - May need liver function tests for those with hepatic abnormalities before initiating treatment
 - May need to monitor blood count during treatment for those with blood dyscrasias, leucopenia, or granulocytopenia
 - Since some antidepressants such as mirtazapine can be associated with significant weight gain, before starting treatment, weigh all patients and determine if the patient is already overweight ($BMI >25.0\text{--}29.9$) or obese ($BMI \geq 30$)
 - Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose $100\text{--}125\text{ mg/dL}$), diabetes (fasting plasma glucose $>126\text{ mg/dL}$), or dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management
- ✿ Monitor weight and BMI during treatment
- ✿ While giving a drug to a patient who has gained $>5\%$ of initial weight, consider evaluating for the presence of pre-diabetes, diabetes, or dyslipidemia, or consider switching to a different antidepressant

Notable Side Effects

- Dry mouth, constipation, increased appetite, weight gain
- Sedation, dizziness, abnormal dreams, confusion
- Flu-like symptoms (may indicate low white blood cell or granulocyte count)
- Change in urinary function
- Hypotension



Life-Threatening or Dangerous Side Effects

- Rare seizures
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Many experience and/or can be significant in amount

Sedation



- Many experience and/or can be significant in amount

What to Do About Side Effects

- Wait
- Wait
- Wait
- Switch to another drug

Best Augmenting Agents for Side Effects

- Often best to try another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
- Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Trazodone or a hypnotic for insomnia
- Many side effects cannot be improved with an augmenting agent

SIDE EFFECTS

How Drug Causes Side Effects

- Most side effects are immediate but often go away with time
- ✿ Histamine 1 receptor antagonism may explain sedative effects
- ✿ Histamine 1 receptor antagonism plus 5HT2C antagonism may explain some aspects of weight gain

- Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of mirtazapine

DOSING AND USE

Usual Dosage Range

- 15–45 mg at night

Dosage Forms

- Tablet 15 mg scored, 30 mg scored, 45 mg
- SolTab disintegrating tablet 15 mg, 30 mg, 45 mg

How to Dose

- Initial 15 mg/day in the evening; increase every 1–2 weeks until desired efficacy is reached; maximum generally 45 mg/day



Dosing Tips

- Sedation may not worsen as dose increases
- Breaking a 15-mg tablet in half and administering 7.5 mg dose may actually increase sedation
- Some patients require more than 45 mg daily, including up to 90 mg in difficult patients who tolerate these doses
- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar disorder and switch to a mood stabilizer or an atypical antipsychotic

Overdose

- Rarely lethal; all fatalities have involved other medications; symptoms include sedation, disorientation, memory impairment, rapid heartbeat

Long-Term Use

- Safe

Habit Forming

- Not expected

How to Stop

- Taper is prudent to avoid withdrawal effects, but tolerance, dependence, and withdrawal effects not reliably reported

Pharmacokinetics

- Half-life 20–40 hours
- Substrate for CYP450 2D6, 3A4, and possibly also CYP450 1A2
- Food does not affect absorption



Drug Interactions

- Tramadol increases the risk of seizures in patients taking an antidepressant
- No significant pharmacokinetic drug interactions
- Can cause a fatal "serotonin syndrome" when combined with MAOIs, so do not use with MAOIs or for at least 14 days after MAOIs are stopped
- Do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing mirtazapine



Other Warnings/ Precautions

- Drug may lower white blood cell count (rare; may not be increased compared to other antidepressants but controlled studies lacking; not a common problem reported in postmarketing surveillance)
- Drug may increase cholesterol
- May cause photosensitivity
- Avoid alcohol, which may increase sedation and cognitive and motor effects
- Use with caution in patients with history of seizures
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately

- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is taking an MAOI
- If there is a proven allergy to mirtazapine

SPECIAL POPULATIONS

Renal Impairment

- Drug should be used with caution

Hepatic Impairment

- Drug should be used with caution
- May require lower dose

Cardiac Impairment

- Drug should be used with caution
- The potential risk of hypotension should be considered

Elderly

- Some patients may tolerate lower doses better
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Safety and efficacy have not been established



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including

the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001

- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy

Breast Feeding

- Unknown if mirtazapine is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients, this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients particularly concerned about sexual side effects
- Patients with symptoms of anxiety
- Patients on concomitant medications
- As an augmenting agent to boost the efficacy of other antidepressants

Potential Disadvantages

- Patients particularly concerned about gaining weight
- Patients with low energy

Primary Target Symptoms

- Depressed mood
- Sleep disturbance
- Anxiety



Pearls

- ✿ Adding alpha 2 antagonism to agents that block serotonin and/or norepinephrine reuptake may be synergistic for severe depression
- Adding mirtazapine to venlafaxine or SSRIs may reverse drug-induced anxiety and insomnia
- Adding mirtazapine's 5HT3 antagonism to venlafaxine or SSRIs may reverse drug-induced nausea, diarrhea, stomach cramps, and gastrointestinal side effects
- SSRIs, venlafaxine, bupropion, phentermine, or stimulants may mitigate mirtazapine-induced weight gain
- If weight gain has not occurred by week 6 of treatment, it is less likely for there to be significant weight gain

- Has been demonstrated to have an earlier onset of action than SSRIs
- ✿ Does not affect the CYP450 system, and so may be preferable in patients requiring concomitant medications
- Preliminary evidence suggests efficacy as an augmenting agent to haloperidol in treating negative symptoms of schizophrenia
- Anecdotal reports of efficacy in recurrent brief depression
- Weight gain as a result of mirtazapine treatment is more likely in women than in men, and before menopause rather than after
- ✿ May cause sexual dysfunction only infrequently
- Patients can have carryover sedation and intoxicated-like feeling if particularly sensitive to sedative side effects when initiating dosing
- Rarely, patients may complain of visual "trails" or after-images on mirtazapine



Suggested Reading

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patients with major depression and symptoms of anxiety. *J Clin Psychiatry* 1998;59:123–7.

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THERAPEUTICS

- Brands**
- Aurorix
 - Arima
 - Manerix

see index for additional brand names

Generic? No



Class

- Neuroscience-based Nomenclature: serotonin, norepinephrine, dopamine reversible enzyme inhibitor (SN-RevEI)
- Reversible inhibitor of monoamine oxidase A (MAO-A) (RIMA)

Commonly Prescribed for

(bold for FDA approved)

- Depression
- Social anxiety disorder



How the Drug Works

- Reversibly blocks MAO-A from breaking down norepinephrine, dopamine, and serotonin
- This presumably boosts noradrenergic, serotonergic, and dopaminergic neurotransmission
- MAO-A inhibition predominates unless significant concentrations of monoamines build up (e.g., due to dietary tyramine), in which case MAO-A inhibition is theoretically reversed

How Long Until It Works

- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped

- Continue treatment until all symptoms are gone (remission)
- Once symptoms gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders may also need to be indefinite

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent, or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer



Best Augmenting Combos for Partial Response or Treatment Resistance

- ✿ Augmentation of MAOIs has not been systematically studied, and this is something for the expert, to be done with caution and with careful monitoring, but may be somewhat less risky with moclobemide than with other MAOIs
- ✿ A stimulant such as d-amphetamine or methylphenidate (with caution; may activate bipolar disorder and suicidal ideation)
- Lithium
- Mood-stabilizing anticonvulsants
- Atypical antipsychotics (with special caution for those agents with monoamine reuptake blocking properties, such as ziprasidone and zotepine)

Tests

- Patients should be monitored for changes in blood pressure

SIDE EFFECTS**How Drug Causes Side Effects**

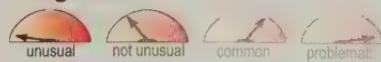
- Theoretically due to increases in monoamines in parts of the brain and body and at receptors other than those that cause therapeutic actions (e.g., unwanted actions of serotonin in sleep centers causing insomnia, unwanted actions of norepinephrine on vascular smooth muscle causing changes in blood pressure)
- Side effects are generally immediate, but immediate side effects often disappear in time

Notable Side Effects

- Insomnia, dizziness, agitation, anxiety, restlessness
- Dry mouth, diarrhea, constipation, nausea, vomiting
- Galactorrhea
- Rare hypertension

**Life-Threatening or Dangerous Side Effects**

- Hypertensive crisis (especially when MAOIs are used with certain tyramine containing foods – reduced risk compared to irreversible MAOIs)
- Induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)
- Seizures

Weight Gain

- Reported but not expected

Sedation

- Occurs in significant minority

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- Switch to an SSRI or newer antidepressant

Best Augmenting Agents for Side Effects

- Trazodone (with caution) for insomnia
- Benzodiazepines for insomnia
- Single oral or sublingual dose of a calcium channel blocker (e.g., nifedipine) for urgent treatment of hypertension due to drug interaction or dietary tyramine
- Many side effects cannot be improved with an augmenting agent

DOSING AND USE**Usual Dosage Range**

- 300–600 mg/day

Dosage Forms

- Tablet 100 mg scored, 150 mg scored

How to Dose

- Initial 300 mg/day in 3 divided doses after a meal; increase dose gradually; maximum dose generally 600 mg/day; minimum dose generally 150 mg/day

**Dosing Tips**

- At higher doses, moclobemide also inhibits MAO-B and thereby loses its selectivity for MAO-A, with uncertain clinical consequences
- Taking moclobemide after meals as opposed to before may minimize the chances of interactions with tyramine
- May be less toxic in overdose than TCAs and older MAOIs
- Clinical duration of action may be longer than biological half-life and allow twice daily dosing in some patients, or even once daily dosing, especially at lower doses

Overdose

- Agitation, aggression, behavioral disturbances, gastrointestinal irritation

Long-Term Use

- MAOIs may lose efficacy long-term

Habit Forming

- Some patients have developed dependence to MAOIs

How to Stop

- Taper not generally necessary

Pharmacokinetics

- Partially metabolized by CYP450 2C19 and 2D6
- Inactive metabolites
- Elimination half-life approximately 1–4 hours
- Clinical duration of action at least 24 hours



Drug Interactions

- Tramadol may increase the risk of seizures in patients taking an MAOI
- Can cause a fatal “serotonin syndrome” when combined with drugs that block serotonin reuptake, so do not use with a serotonin reuptake inhibitor or for 5 half-lives after stopping the serotonin reuptake inhibitor (see Table 1 after Pearls)
- Hypertensive crisis with headache, intracranial bleeding, and death may result from combining MAOIs with sympathomimetic drugs (e.g., amphetamines, methylphenidate, cocaine, dopamine, epinephrine, norepinephrine, and related compounds methyldopa, levodopa, L-tryptophan, L-tyrosine, and phenylalanine)
- Do not combine with another MAOI, alcohol, or guanethidine
- Adverse drug reactions can result from combining MAOIs with tricyclic/tetracyclic antidepressants and related compounds, including carbamazepine, cyclobenzaprine, and mirtazapine, and should be avoided except by experts to treat difficult cases
- MAOIs in combination with spinal anesthesia may cause combined hypotensive effects
- Combination of MAOIs and CNS depressants may enhance sedation and hypotension
- Cimetidine may increase plasma concentrations of moclobemide
- Moclobemide may enhance the effects of NSAIDs such as ibuprofen
- Risk of hypertensive crisis may be increased if moclobemide is used concurrently with levodopa or other dopaminergic agents



Other Warnings/ Precautions

- Use still requires low tyramine diet, although more tyramine may be tolerated with moclobemide than with other MAOIs before eliciting a hypertensive reaction (see Table 2 after Pearls)
- Patient and prescriber must be vigilant to potential interactions with any drug, including antihypertensives and over-the-counter cough/cold preparations
- Over-the-counter medications to avoid include cough and cold preparations, including those containing dextromethorphan, nasal decongestants (tablets, drops, or spray), hay-fever medications, sinus medications, asthma inhalant medications, anti-appetite medications, weight reducing preparations, “pep” pills (see Table 3 after Pearls)
- Use cautiously in hypertensive patients
- Moclobemide is not recommended for use in patients who cannot be monitored closely
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is taking meperidine (pethidine)
- If patient is taking a sympathomimetic agent or taking guanethidine
- If patient is taking another MAOI
- If patient is taking any agent that can inhibit serotonin reuptake (e.g., SSRIs, sibutramine, tramadol, milnacipran, duloxetine, venlafaxine, clomipramine, etc.)
- If patient is in an acute confusional state
- If patient has pheochromocytoma or thyrotoxicosis
- If patient has frequent or severe headaches

- If patient is undergoing elective surgery and requires general anesthesia
- If there is a proven allergy to moclobemide

SPECIAL POPULATIONS

Renal Impairment

- Use with caution

Hepatic Impairment

- Plasma concentrations are increased
- May require one-half to one-third of usual adult dose

Cardiac Impairment

- Cardiac impairment may require lower than usual adult dose
- Patients with angina pectoris or coronary artery disease should limit their exertion

Elderly

- Elderly patients may have greater sensitivity to adverse effects
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Not recommended for use in children under age 18
- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients



Pregnancy

- Not generally recommended for use during pregnancy, especially during first trimester

- Should evaluate patient for treatment with an antidepressant with a better risk/benefit ratio

Breast Feeding

- Some drug is found in mother's breast milk
- Effects on infant are unknown
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Should evaluate patient for treatment with an antidepressant with a better risk/benefit ratio

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Atypical depression
- Severe depression
- Treatment-resistant depression or anxiety disorders

Potential Disadvantages

- Patients noncompliant with dietary restrictions, concomitant drug restrictions, and twice daily dosing after meals

Primary Target Symptoms

- Depressed mood



Pearls

- MAOIs are generally reserved for second-line use after SSRIs, SNRIs, and combinations of newer antidepressants have failed
- Patient should be advised not to take any prescription or over-the-counter drugs without consulting his/her doctor because of possible drug interactions with the MAOI
- Headache is often the first symptom of hypertensive crisis
- Moclobemide has a much reduced risk of interactions with tyramine than nonselective MAOIs

- Especially at higher doses of moclobemide, foods with high tyramine need to be avoided (see Table 2)
- The rigid dietary restrictions may reduce compliance
- ✿ May be a safer alternative to classical irreversible nonselective MAO-A and MAO-B inhibitors with less propensity for tyramine and drug interactions and hepatotoxicity (although not entirely free of interactions)
- May not be as effective at low doses, and may have more side effects at higher doses
- Moclobemide's profile at higher doses may be more similar to classical MAOIs
- MAOIs are a viable second-line treatment option in depression, but are not frequently used
- ✿ Myths about the danger of dietary tyramine can be exaggerated, but prohibitions against concomitant drugs often not followed closely enough
- Orthostatic hypotension, insomnia, and sexual dysfunction are often the most troublesome common side effects
- ✿ MAOIs should be for the expert, especially if combining with agents of potential risk (e.g., stimulants, trazodone, TCAs)
- ✿ MAOIs should not be neglected as therapeutic agents for the treatment-resistant
- Although generally prohibited, a heroic but potentially dangerous treatment for severely treatment-resistant patients is for an expert to give a tricyclic/tetracyclic antidepressant other than clomipramine simultaneously with an MAOI for patients who fail to respond to numerous other antidepressants
- Use of MAOIs with clomipramine is always prohibited because of the risk of serotonin syndrome and death
- Amoxapine may be the preferred tricyclic/tetracyclic antidepressant to combine with an MAOI in heroic cases due to its theoretically protective 5HT2A antagonist properties
- If this option is elected, start the MAOI with the tricyclic/tetracyclic antidepressant simultaneously at low doses after appropriate drug washout, then alternately increase doses of these agents every few days to a week as tolerated
- Although very strict dietary and concomitant drug restrictions must be observed to prevent hypertensive crises and serotonin syndrome, the most common side effects of MAOI and tricyclic/tetracyclic combinations may be weight gain and orthostatic hypotension

Table 1. Drugs contraindicated due to risk of serotonin syndrome/toxicity

Do Not Use:			
Antidepressants	Drugs of Abuse	Opioids	Other
SSRIs	MDMA (ecstasy)	Meperidine	Non-subcutaneous sumatriptan
SNRIs	Cocaine	Tramadol	Chlorpheniramine
Clomipramine	Methamphetamine	Methadone	Brompheniramine
St. John's wort	High-dose or injected amphetamine	Fentanyl	Dextromethorphan
			Procarbazine?

MOCLOBEMIDE (continued)

Table 2. Dietary guidelines for patients taking MAOIs

Foods to avoid*	Foods allowed
Dried, aged, smoked, fermented, spoiled, or improperly stored meat, poultry, and fish	Fresh or processed meat, poultry, and fish; properly stored pickled or smoked fish
Broad bean pods	All other vegetables
Aged cheeses	Processed cheese slices, cottage cheese, ricotta cheese, yogurt, cream cheese
Tap and unpasteurized beer	Canned or bottled beer and alcohol
Marmite	Brewer's and baker's yeast
Sauerkraut, kimchee	
Soy products/tofu	Peanuts
Banana peel	Bananas, avocados, raspberries
Tyramine-containing nutritional supplement	

*Not necessary for 6-mg transdermal or low-dose oral selegiline

Table 3. Drugs that boost norepinephrine: should only be used with caution with MAOIs

Use With Caution:			
Decongestants	Stimulants	Antidepressants with norepinephrine reuptake inhibition	Other
Phenylephrine	Amphetamines	Most tricyclics	Phentermine
Pseudoephedrine	Methylphenidate	NRIs	Local anesthetics containing vasoconstrictors
	Cocaine	NDRIs	
	Methamphetamine		
	Modafinil		Tapentadol
	Armodafinil		



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role of monoamine oxidase inhibitors. *J Psychiatry Neurosci* 1997;22:127-31.

Lippman SB, Nash K. Monoamine oxidase inhibitor update. Potential adverse food and drug interactions. *Drug Saf* 1990;5:195-204.

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THERAPEUTICS

- Brands**
- Provigil
 - Alertec
 - Modiodal

see index for additional brand names

Generic? Yes



Class

- Neuroscience-based Nomenclature: dopamine reuptake inhibitor (D-RI)
- Wake-promoting

Commonly Prescribed for

(bold for FDA approved)

- Reducing excessive sleepiness in patients with narcolepsy and shift work sleep disorder
- Reducing excessive sleepiness in patients with obstructive sleep apnea/hypopnea syndrome (OSAHS) (adjunct to standard treatment for underlying airway obstruction)
- Attention deficit hyperactivity disorder (ADHD)
- Fatigue and sleepiness in depression
- Fatigue in multiple sclerosis
- Bipolar depression



How the Drug Works

- Unknown, but clearly different from classical stimulants such as methylphenidate and amphetamine
- Binds to and requires the presence of the dopamine transporter; also requires the presence of alpha adrenergic receptors
- Hypothetically acts as an inhibitor of the dopamine transporter
- Increases neuronal activity selectively in the hypothalamus
- Presumably enhances activity in hypothalamic wakefulness center (TMN, tuberomammillary nucleus) within the hypothalamic sleep-wake switch by an unknown mechanism
- Activates TMN neurons that release histamine
- Activates other hypothalamic neurons that release orexin/hypocretin

How Long Until It Works

- Can immediately reduce daytime sleepiness and improve cognitive task performance within 2 hours of first dosing

- Can take several days to optimize dosing and clinical improvement

If It Works

- Improves daytime sleepiness and may improve attention as well as fatigue
- Does not generally prevent one from falling asleep when needed
- May not completely normalize wakefulness
- Treat until improvement stabilizes and then continue treatment indefinitely as long as improvement persists (studies support at least 12 weeks of treatment)

If It Doesn't Work

- Change dose; some patients do better with an increased dose but some actually do better with a decreased dose
- Augment or consider an alternative treatment for daytime sleepiness, fatigue, or ADHD



Best Augmenting Combos for Partial Response or Treatment Resistance

- Modafinil is itself an adjunct to standard treatments for obstructive sleep apnea/hypopnea syndrome (OSAHS); if continuous positive airway pressure (CPAP) is the treatment of choice, a maximal effort to treat first with CPAP should be made prior to initiating modafinil and CPAP should be continued after initiation of modafinil
- Modafinil is itself an augmenting therapy to antidepressants for residual sleepiness and fatigue in major depressive disorder
- Best to attempt another monotherapy prior to augmenting with other drugs in the treatment of sleepiness associated with sleep disorders or problems concentrating in ADHD
- Combination of modafinil with stimulants such as methylphenidate or amphetamine or with atomoxetine for ADHD has not been systematically studied
- However, such combinations may be useful options for experts, with close monitoring, when numerous monotherapies for sleepiness or ADHD have failed

Tests

- None for healthy individuals

SIDE EFFECTS

How Drug Causes Side Effects

- Unknown
- CNS side effects presumably due to excessive CNS actions on various neurotransmitter systems

Notable Side Effects

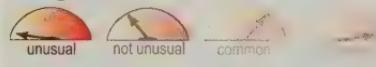
- ✖ Headache (dose-dependent)
- Anxiety, nervousness, insomnia
 - Dry mouth, diarrhea, nausea, anorexia
 - Pharyngitis, rhinitis, infection
 - Hypertension
 - Palpitations



Life-Threatening or Dangerous Side Effects

- Transient EKG ischemic changes in patients with mitral valve prolapse or left ventricular hypertrophy have been reported (rare)
- Rare activation of (hypo)mania, anxiety, hallucinations, or suicidal ideation
- Rare severe dermatologic reactions (Stevens-Johnson syndrome and others)
- Angioedema, anaphylactoid reactions, and multi-organ hypersensitivity reactions have been reported

Weight Gain



- Reported but not expected

Sedation



- Reported but not expected
- Patients are usually awakened and some may be activated

What to Do About Side Effects

- Wait
- Lower the dose
- Give only once daily
- Give smaller split doses 2 or more times daily
- For activation or insomnia, do not give in the evening
- If unacceptable side effects persist, discontinue use
- For life-threatening or dangerous side effects, discontinue immediately (e.g., at first sign of a drug-related rash)

Best Augmenting Agents for Side Effects

- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 200 mg/day in the morning

Dosage Forms

- Tablet 100 mg, 200 mg (scored)

How to Dose

- Titration up or down only necessary if not optimally efficacious at the standard starting dose of 200 mg once a day in the morning



Dosing Tips

- ✖ For sleepiness, more may be more: higher doses (200–800 mg/day) may be better than lower doses (50–200 mg/day) in patients with daytime sleepiness in sleep disorders
- ✖ For problems concentrating and fatigue, less may be more: lower doses (50–200 mg/day) may be paradoxically better than higher doses (200–800 mg/day) in some patients
- At high doses, may slightly induce its own metabolism, possibly by actions of inducing CYP450 3A4
 - Dose may creep upward in some patients with long-term treatment due to autoinduction; drug holiday may restore efficacy at original dose

Overdose

- No fatalities; agitation, insomnia, increase in hemodynamic parameters
- Postmarketing experience includes CNS symptoms, such as restlessness, disorientation, confusion, excitation, and hallucinations; digestive changes, such as nausea and diarrhea; and cardiovascular changes, such as tachycardia, bradycardia, hypertension, and chest pain

Long-Term Use

- Efficacy in reducing excessive sleepiness in sleep disorders has been demonstrated in 9- to 12-week trials
- Unpublished data show safety for up to 136 weeks

- The need for continued treatment should be reevaluated periodically

Habit Forming

- Schedule IV; may have some potential for abuse but unusual in clinical practice

How to Stop

- Taper not necessary; patients may have sleepiness on discontinuation

Pharmacokinetics

- Metabolized by the liver
- Excreted renally
- Elimination half-life 10–12 hours
- Inhibits CYP450 2C19 (and perhaps 2C9)
- Induces CYP450 3A4 (and slightly 1A2 and 2B6)



Drug Interactions

- May increase plasma levels of drugs metabolized by CYP450 2C19 (e.g., diazepam, phenytoin, propranolol)
- Modafinil may increase plasma levels of CYP450 2D6 substrates such as TCAs and SSRIs, perhaps requiring downward dose adjustments of these agents
- Modafinil may decrease plasma levels of CYP450 3A4 substrates such as ethinyl estradiol and triazolam
- Due to induction of CYP450 3A4, effectiveness of steroidal contraceptives may be reduced by modafinil, including 1 month after discontinuation
- Inducers or inhibitors of CYP450 3A4 may affect levels of modafinil (e.g., carbamazepine may lower modafinil plasma levels; fluvoxamine and fluoxetine may raise modafinil plasma levels)
- Modafinil may slightly reduce its own levels by autoinduction of CYP450 3A4
- Modafinil may increase clearance of drugs dependent on CYP450 1A2 and reduce their plasma levels
- Patients on modafinil and warfarin should have prothrombin times monitored
- Methylphenidate may delay absorption of modafinil by an hour
- However, coadministration with methylphenidate does not significantly change the pharmacokinetics of either modafinil or methylphenidate
- Coadministration with dextroamphetamine also does not

significantly change the pharmacokinetics of either modafinil or dextroamphetamine

- Interaction studies with MAOIs have not been performed, but MAOIs can be given with modafinil by experts with cautious monitoring



Other Warnings/ Precautions

- Patients with history of drug abuse should be monitored closely
- Modafinil may cause CNS effects similar to those caused by other CNS agents (e.g., changes in mood and, theoretically, activation of psychosis, mania, or suicidal ideation)
- Modafinil should be used in patients with sleep disorders that have been completely evaluated for narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), and shift work sleep disorder
- In OSAHS patients for whom continuous positive airway pressure (CPAP) is the treatment of choice, a maximal effort to treat first with CPAP should be made prior to initiating modafinil, and then CPAP should be continued after initiating modafinil
- The effectiveness of steroidal contraceptives may be reduced when used with modafinil and for 1 month after discontinuation of modafinil
- Modafinil is not a replacement for sleep

Do Not Use

- If patient has severe hypertension
- If patient has cardiac arrhythmias
- If there is a proven allergy to modafinil

SPECIAL POPULATIONS

Renal Impairment

- Use with caution; dose reduction is recommended

Hepatic Impairment

- Reduce dose by half in severely impaired patients

Cardiac Impairment

- Use with caution

- Not recommended for use in patients with a history of left ventricular hypertrophy, ischemic EKG changes, chest pain, arrhythmias, or recent myocardial infarction

Elderly

- Limited experience in patients over 65
- Clearance of modafinil may be reduced in elderly patients



Children and Adolescents

- Safety and efficacy not established under age 16
- Can be used cautiously by experts for children and adolescents



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Intrauterine growth restriction and spontaneous abortion have been reported with armodafinil and modafinil
- In animal studies, developmental toxicity was observed at clinically relevant plasma exposures of armodafinil and modafinil
- Use in women of childbearing potential requires weighing potential benefits to the mother against potential risks to the fetus
- Generally, modafinil should be discontinued prior to anticipated pregnancies

Breast Feeding

- Unknown if modafinil is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- Recommended either to discontinue drug or bottle feed

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Selective for areas of brain involved in sleep/wake promotion
- Less activating and less abuse potential than stimulants

Potential Disadvantages

- May not work as well as stimulants in some patients

Primary Target Symptoms

- Sleepiness
- Concentration
- Physical and mental fatigue



Pearls

- Anecdotal usefulness for jet lag short-term (off label)
- Modafinil is not a replacement for sleep
- The treatment for sleep deprivation is sleep, not modafinil
- Controlled studies suggest modafinil improves attention in OSAHS, shift work sleep disorder, and ADHD (both children and adults), but controlled studies of attention have not been performed in major depressive disorder
- May be useful to treat fatigue in patients with depression as well as other disorders, such as multiple sclerosis, myotonic dystrophy, HIV/AIDS
- In depression, modafinil's actions on fatigue appear to be independent of actions (if any) on mood
- In depression, modafinil's actions on sleepiness also appear to be independent of actions (if any) on mood but may be linked to actions on fatigue or on global functioning
- Several controlled studies in depression show improvement in sleepiness or global functioning, especially for depressed patients with sleepiness and fatigue
- May be useful adjunct to mood stabilizers for bipolar depression
- May be useful in treating sleepiness associated with opioid analgesia, particularly in end-of-life management
- Subjective sensation associated with modafinil is usually one of normal

wakefulness, not of stimulation, although jitteriness can rarely occur

- Anecdotally, some patients may experience wearing off of efficacy over time, especially for off-label uses, with restoration of efficacy after a drug holiday; such wearing off is less likely with intermittent dosing

✳ Compared to stimulants, modafinil has a novel mechanism of action, novel therapeutic

uses, and less abuse potential, but is often inaccurately classified as a stimulant

- Alpha 1 antagonists such as prazosin may block the therapeutic actions of modafinil
- The active R enantiomer of modafinil, called armodafinil, is also available



Suggested Reading

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THERAPEUTICS

Brands • Dutonin
see index for additional brand names

Generic? Yes

**Class**

- Neuroscience-based Nomenclature: serotonin receptor antagonist
- SARI (serotonin 2 antagonist/reuptake inhibitor); antidepressant

Commonly Prescribed for

(bold for FDA approved)

- Depression
- Relapse prevention in major depressive disorder
- Panic disorder
- Posttraumatic stress disorder (PTSD)

**How the Drug Works**

- Blocks serotonin 2A receptors potently
- Blocks serotonin reuptake pump (serotonin transporter) and norepinephrine reuptake pump (norepinephrine transporter) less potently

How Long Until It Works

- Can improve insomnia and anxiety early after initiating dosing
- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Continue treatment until all symptoms are gone (remission)
- Once symptoms gone, continue treating for 1 year for the first episode of depression

- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders may also need to be indefinite

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some patients who have an initial response may relapse even though they continue treatment, sometimes called "poop-out"
- Consider increasing dose, switching to another agent, or adding an appropriate augmenting agent
- Consider psychotherapy, especially cognitive-behavioral psychotherapies, which have been specifically shown to enhance nefazodone's antidepressant actions
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer

**Best Augmenting Combos for Partial Response or Treatment Resistance**

- Venlafaxine and escitalopram may be the best tolerated when switching or augmenting with a serotonin reuptake inhibitor, as neither is a potent CYP450 2D6 inhibitor (use combinations of antidepressants with caution as this may activate bipolar disorder and suicidal ideation)
- Modafinil, especially for fatigue, sleepiness, and lack of concentration
- Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression, or treatment-resistant depression
- Benzodiazepines for anxiety, but give alprazolam cautiously with nefazodone as alprazolam levels can be much higher in the presence of nefazodone
- Classically, lithium, buspirone, or thyroid hormone

Tests

- ★ Liver function testing is not required but is often prudent given the small but finite risk of serious hepatotoxicity
- ★ However, to date no clinical strategy, including routine liver function tests, has been identified to reduce the risk of irreversible liver failure

Weight Gain



- Reported but not expected

Sedation



- Many experience and/or can be significant in amount

What to Do About Side Effects

- Wait
- Wait
- Wait
- Take once daily at night to reduce daytime sedation
- Lower the dose and try titrating again more slowly as tolerated
- Switch to another agent

Best Augmenting Agents for Side Effects

- Often best to try another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
- Many side effects cannot be improved with an augmenting agent
- Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of nefazodone

SIDE EFFECTS

How Drug Causes Side Effects

- Blockade of alpha adrenergic 1 receptors may explain dizziness, sedation, and hypotension
- A metabolite of nefazodone, mCPP (meta-chloro-phenyl-piperazine), can cause side effects if its levels rise significantly
- ★ If CYP450 2D6 is absent (7% of Caucasians lack CYP450 2D6) or inhibited (concomitant treatment with CYP450 2D6 inhibitors such as fluoxetine or paroxetine), increased levels of mCPP can form, leading to stimulation of 5HT2C receptors and causing dizziness, insomnia, and agitation
- Most side effects are immediate but often go away with time

Notable Side Effects

- Nausea, dry mouth, constipation, dyspepsia, increased appetite
- Headache, dizziness, vision changes, sedation, insomnia, agitation, confusion, memory impairment
- Ataxia, paresthesia, asthenia
- Cough increased
- Rare postural hypotension



Life-Threatening or Dangerous Side Effects

- Rare seizures
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)
- Rare priapism (no causal relationship established)
- Hepatic failure requiring liver transplant and/or fatal

DOSING AND USE

Usual Dosage Range

- 300–600 mg/day

Dosage Forms

- Tablet 50 mg, 100 mg scored, 150 mg scored, 200 mg, 250 mg

How to Dose

- Initial dose 100 mg twice a day; increase by 100–200 mg/day each week until desired efficacy is reached; maximum dose 600 mg twice a day



Dosing Tips

- Take care switching from or adding to SSRIs (especially fluoxetine or paroxetine) because of side effects due to the drug interaction
- Do not underdose the elderly
- Normally twice daily dosing, especially when initiating treatment
- Patients may tolerate all dosing once daily at night once titrated
- Often much more effective at 400–600 mg/day than at lower doses if tolerated
- Slow titration can enhance tolerability when initiating dosing

Overdose

- Rarely lethal; sedation, nausea, vomiting, low blood pressure

Long-Term Use

- Safe

Habit Forming

- No

How to Stop

- Taper is prudent to avoid withdrawal effects, but problems in withdrawal not common

Pharmacokinetics

- Half-life of parent compound is 2–4 hours
- Half-life of active metabolites up to 12 hours
- Inhibits CYP450 3A4



Drug Interactions

- Tramadol increases the risk of seizures in patients taking an antidepressant
 - May interact with SSRIs such as paroxetine, fluoxetine, and others that inhibit CYP450 2D6
- * Since a metabolite of nefazodone, mCPP, is a substrate of CYP450 2D6, combination of 2D6 inhibitors with nefazodone will raise mCPP levels, leading to stimulation

of 5HT2C receptors and causing dizziness and agitation

- Can cause a fatal “serotonin syndrome” when combined with MAOIs, so do not use with MAOIs or for at least 14 days after MAOIs are stopped
- Do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing nefazodone
- Via CYP450 3A4 inhibition, nefazodone may increase the half-life of alprazolam and triazolam, so their dosing may need to be reduced by half or more
- Via CYP450 3A4, nefazodone may increase plasma concentrations of buspirone, so buspirone dose may need to be reduced
- Via CYP450 3A4 inhibition, nefazodone could theoretically increase concentrations of certain cholesterol lowering HMG CoA reductase inhibitors, especially simvastatin, atorvastatin, and lovastatin, but not pravastatin or fluvastatin, which would increase the risk of rhabdomyolysis; thus, coadministration of nefazodone with certain HMG CoA reductase inhibitors should proceed with caution
- Via CYP450 3A4 inhibition, nefazodone could theoretically increase the concentrations of pimozide, and cause QTc prolongation and dangerous cardiac arrhythmias
- Nefazodone may reduce clearance of haloperidol, so haloperidol dose may need to be reduced
- It is recommended to discontinue nefazodone prior to elective surgery because of the potential for interaction with general anesthetics



Other Warnings/ Precautions

- * Hepatotoxicity, sometimes requiring liver transplant and/or fatal, has occurred with nefazodone use. Risk may be one in every 250,000 to 300,000 patient years. Patients should be advised to report symptoms such as jaundice, dark urine, loss of appetite, nausea, and abdominal pain to prescriber immediately. If patient develops signs of hepatocellular injury, such as increased serum AST or serum ALPT levels >3 times the upper limit of normal, nefazodone treatment should be discontinued.

- ✿ No risk factor yet predicts who will develop irreversible liver failure with nefazodone and no clinical strategy, including routine monitoring of liver function tests, is known to reduce the risk of liver failure
- Use with caution in patients with history of seizures
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is taking an MAOI
- If patient has acute hepatic impairment or elevated baseline serum transaminases
- If patient was previously withdrawn from nefazodone treatment due to hepatic injury
- If patient is taking pimozide, as nefazodone could raise pimozide levels and increase QTc interval, perhaps causing dangerous arrhythmia
- If patient is taking carbamazepine, as this agent can dramatically reduce nefazodone levels and thus interfere with its antidepressant actions
- If there is a proven allergy to nefazodone

SPECIAL POPULATIONS

Renal Impairment

- No dose adjustment necessary

Hepatic Impairment

- Contraindicated in patients with known hepatic impairment

Cardiac Impairment

- Use in patients with cardiac impairment has not been studied, so use with caution because of risk of orthostatic hypotension

Elderly

- Recommended to initiate treatment at half the usual adult dose, but to follow the same titration schedule as with younger patients, including same ultimate dose
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older.



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Safety and efficacy have not been established
- Preliminary research indicates efficacy and tolerability of nefazodone in children and adolescents with depression



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester
- Must weigh the risk of treatment (first trimester fetal development, third trimester

newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child

- For many patients this may mean continuing treatment during pregnancy

Breast Feeding

- Unknown if nefazodone is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- Trace amounts may be present in nursing children whose mothers are on nefazodone
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients, this may mean continuing treatment during breast feeding

- Patients with SSRI-induced sexual dysfunction

Potential Disadvantages

- Patients who have difficulty with a long titration period or twice daily dosing
- Patients with hepatic impairment

Primary Target Symptoms

- Depressed mood
- Sleep disturbance
- Anxiety



Pearls

- Preliminary data for efficacy in panic disorder and PTSD
- Fluoxetine and paroxetine may not be tolerated when switching or augmenting
- For elderly patients with early dementia and agitated depression, consider nefazodone in the morning and additional trazodone at night
- Anecdotal reports suggest that nefazodone may be effective in treating PMDD
- Studies suggest that cognitive behavioral psychotherapy enhances the efficacy of nefazodone in chronic depression
- Risk of hepatotoxicity makes this agent a second-line choice and has led to its withdrawal from some markets, including the withdrawal of Serzone from the US market
- Rarely, patients may complain of visual "trails" or after-images on nefazodone

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Depressed patients with anxiety or insomnia who do not respond to other antidepressants



Suggested Reading

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Khouzam HR. The antidepressant nefazodone. A review of its pharmacology, clinical efficacy, adverse effects, dosage, and administration. *J Psychosocial Nursing Ment Health Serv* 2000;38:20-5.

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THERAPEUTICS

Brands • Pamelor
see index for additional brand names

Generic? Yes

**Class**

- Neuroscience-based Nomenclature: serotonin, norepinephrine reuptake inhibitor (SN-RI)
- Tricyclic antidepressant (TCA)
- Predominantly a norepinephrine/noradrenaline reuptake inhibitor

Commonly Prescribed for

(bold for FDA approved)

- Major depressive disorder
- Anxiety
- Insomnia
- Neuropathic pain/chronic pain
- Treatment-resistant depression

**How the Drug Works**

- Boosts neurotransmitter norepinephrine/noradrenaline
- Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing noradrenergic neurotransmission
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, nortriptyline can increase dopamine neurotransmission in this part of the brain
- A more potent inhibitor of norepinephrine reuptake pump than serotonin reuptake pump (serotonin transporter)
- At high doses may also boost neurotransmitter serotonin and presumably increase serotonergic neurotransmission

How Long Until It Works

- May have immediate effects in treating insomnia or anxiety
- Onset of therapeutic actions usually not immediate, but often delayed 2 to 4 weeks
- If it is not working within 6 to 8 weeks for depression, it may require a dosage increase or it may not work at all

- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment of depression is complete remission of current symptoms as well as prevention of future relapses
- The goal of treatment of chronic neuropathic pain is to reduce symptoms as much as possible, especially in combination with other treatments
- Treatment of depression most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Treatment of chronic neuropathic pain may reduce symptoms, but rarely eliminates them completely, and is not a cure since symptoms can recur after medicine is stopped
- Continue treatment of depression until all symptoms are gone (remission)
- Once symptoms of depression are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders and chronic pain may also need to be indefinite, but long-term treatment is not well studied in these conditions

If It Doesn't Work

- Many depressed patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other depressed patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer



Best Augmenting Combos for Partial Response or Treatment Resistance

- Lithium, buspirone, thyroid hormone (for depression)
- Gabapentin, tiagabine, other anticonvulsants, even opiates if done by experts while monitoring carefully in difficult cases (for chronic pain)

Tests

- Baseline ECG is recommended for patients over age 50
- * Monitoring of plasma drug levels is available**
- * Since tricyclic and tetracyclic antidepressants are frequently associated with weight gain, before starting treatment, weigh all patients and determine if the patient is already overweight (BMI 25.0–29.9) or obese (BMI ≥30)**
- Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–125 mg/dL), diabetes (fasting plasma glucose >126 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management
- * Monitor weight and BMI during treatment**
- * While giving a drug to a patient who has gained >5% of initial weight, consider evaluating for the presence of pre-diabetes, diabetes, or dyslipidemia, or consider switching to a different antidepressant**
- EKGs may be useful for selected patients (e.g., those with personal or family history of QTc prolongation; cardiac arrhythmia; recent myocardial infarction; uncompensated heart failure; or taking agents that prolong QTc interval such as pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin, etc.)
- Patients at risk for electrolyte disturbances (e.g., patients on diuretic therapy) should have baseline and periodic serum potassium and magnesium measurements

SIDE EFFECTS

How Drug Causes Side Effects

- Anticholinergic activity may explain sedative effects, dry mouth, constipation, and blurred vision
- Sedative effects and weight gain may be due to antihistamine properties
- Blockade of alpha adrenergic 1 receptors may explain dizziness, sedation, and hypotension
- Cardiac arrhythmias and seizures, especially in overdose, may be caused by blockade of ion channels

Notable Side Effects

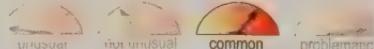
- Blurred vision, constipation, urinary retention, increased appetite, dry mouth, nausea, diarrhea, heartburn, unusual taste in mouth, weight gain
- Fatigue, weakness, dizziness, sedation, headache, anxiety, nervousness, restlessness
- Sexual dysfunction (impotence, change in libido)
- Sweating, rash, itching



Life-Threatening or Dangerous Side Effects

- Paralytic ileus, hyperthermia (TCAs + anticholinergic agents)
- Lowered seizure threshold and rare seizures
- Orthostatic hypotension, sudden death, arrhythmias, tachycardia
- QTc prolongation
- Hepatic failure, extrapyramidal symptoms
- Increased intraocular pressure
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Many experience and/or can be significant in amount
- Can increase appetite and carbohydrate craving

Sedation



- Many experience and/or can be significant in amount
- Tolerance to sedative effect may develop with long-term use

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- Switch to an SSRI or newer antidepressant

Best Augmenting Agents for Side Effects

- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 75–150 mg/day once daily or in up to 4 divided doses (for depression)
- 50–150 mg/day (for chronic pain)

Dosage Forms

- Capsule 10 mg, 25 mg, 50 mg, 75 mg
- Liquid 10 mg/5mL

How to Dose

- Initial 10–25 mg/day at bedtime; increase by 25 mg every 3–7 days; can be dosed once daily or in divided doses; maximum dose 300 mg/day
- When treating nicotine dependence, nortriptyline should be initiated 10–28 days before cessation of smoking to achieve steady drug states



Dosing Tips

- If given in a single dose, should generally be administered at bedtime because of its sedative properties
- If given in split doses, largest dose should generally be given at bedtime because of its sedative properties
- If patients experience nightmares, split dose and do not give large dose at bedtime
- Patients treated for chronic pain may require only lower doses

- Risk of seizure increases with dose
- Monitoring plasma levels of nortriptyline is recommended in patients who do not respond to the usual dose or whose treatment is regarded as urgent
- Some formulations of nortriptyline contain sodium bisulphite, which may cause allergic reactions in some patients, perhaps more frequently in asthmatics
- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar disorder, and switch to a mood stabilizer or an atypical antipsychotic

Overdose

- Death may occur; CNS depression, convulsions, cardiac dysrhythmias, severe hypotension, EKG changes, coma

Long-Term Use

- Safe

Habit Forming

- No

How to Stop

- Taper to avoid withdrawal effects
- Even with gradual dose reduction some withdrawal symptoms may appear within the first 2 weeks
- Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation
- If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly

Pharmacokinetics

- Substrate for CYP450 2D6 and 3A4
- Nortriptyline is the active metabolite of amitriptyline, formed by demethylation via CYP450 1A2
- Half-life approximately 36 hours
- Food does not affect absorption



Drug Interactions

- Tramadol increases the risk of seizures in patients taking TCAs
- Use of TCAs with anticholinergic drugs may result in paralytic ileus or hyperthermia

- Fluoxetine, paroxetine, bupropion, duloxetine, and other CYP450 2D6 inhibitors may increase TCA concentrations and cause side effects including dangerous arrhythmias
- Cimetidine may increase plasma concentrations of TCAs and cause anticholinergic symptoms
- Phenothiazines or haloperidol may raise TCA blood concentrations
- May alter effects of antihypertensive drugs; may inhibit hypotensive effects of clonidine
- Use of TCAs with sympathomimetic agents may increase sympathetic activity
- Methylphenidate may inhibit metabolism of TCAs
- Nortriptyline may raise plasma levels of dicumarol
- Activation and agitation, especially following switching or adding antidepressants, may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of nortriptyline
- Because TCAs can prolong QTc interval, use with caution in patients who have hypokalemia and/or hypomagnesemia or who are taking drugs that can induce hypokalemia and/or magnesium (e.g., diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactide)
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents



Other Warnings/ Precautions

- Add or initiate other antidepressants with caution for up to 2 weeks after discontinuing nortriptyline
- Generally, do not use with MAOIs, including 14 days after MAOIs are stopped; do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing nortriptyline, but see Pearls
- Use with caution in patients with history of seizures, urinary retention, angle-closure glaucoma, hyperthyroidism
- TCAs can increase QTc interval, especially at toxic doses, which can be attained not only by overdose but also by combining with drugs that inhibit TCA metabolism via CYP450 2D6, potentially causing torsade de pointes-type arrhythmia or sudden death
- Because TCAs can prolong QTc interval, use with caution in patients who have bradycardia or who are taking drugs that can induce bradycardia (e.g., beta blockers, calcium channel blockers, clonidine, digitalis)

Do Not Use

- If patient is recovering from myocardial infarction
- If patient is taking agents capable of significantly prolonging QTc interval (e.g., pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin)
- If there is a history of QTc prolongation or cardiac arrhythmia, recent acute myocardial infarction, uncompensated heart failure
- If patient is taking drugs that inhibit TCA metabolism, including CYP450 2D6 inhibitors, except by an expert
- If there is reduced CYP450 2D6 function, such as patients who are poor 2D6 metabolizers, except by an expert and at low doses
- If there is a proven allergy to nortriptyline or amitriptyline

SPECIAL POPULATIONS

Renal Impairment

- Use with caution; may need to lower dose
- May need to monitor plasma levels

Hepatic Impairment

- Use with caution
- May need to monitor plasma levels
- May require a lower dose with slower titration

Cardiac Impairment

- Baseline ECG is recommended
- TCAs have been reported to cause arrhythmias, prolongation of conduction time, orthostatic hypotension, sinus tachycardia, and heart failure, especially in the diseased heart
- Myocardial infarction and stroke have been reported with TCAs
- TCAs produce QTc prolongation, which may be enhanced by the existence of bradycardia, hypokalemia, congenital or acquired long QTc interval, which should be evaluated prior to administering nortriptyline
- Use with caution if treating concomitantly with a medication likely to produce prolonged bradycardia, hypokalemia, slowing of intracardiac conduction, or prolongation of the QTc interval
- Avoid TCAs in patients with a known history of QTc prolongation, recent acute myocardial infarction, and uncompensated heart failure
- TCAs may cause a sustained increase in heart rate in patients with ischemic heart disease and may worsen (decrease) heart rate variability, an independent risk of mortality in cardiac populations
- Since SSRIs may improve (increase) heart rate variability in patients following a myocardial infarct and may improve survival as well as mood in patients with acute angina or following a myocardial infarction, these are more appropriate agents for cardiac population than tricyclic/tetracyclic antidepressants

✿ Risk/benefit ratio may not justify use of TCAs in cardiac impairment

Elderly

- Baseline ECG is recommended for patients over age 50
- May be more sensitive to anticholinergic, cardiovascular, hypotensive, and sedative effects
- May require lower dose; it may be useful to monitor plasma levels in elderly patients
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Not recommended for use in children under age 12
- Not intended for use in children under age 6
- Several studies show lack of efficacy of TCAs for depression
- May be used to treat enuresis or hyperactive/impulsive behaviors
- Some cases of sudden death have occurred in children taking TCAs
- Plasma levels may need to be monitored
- Dose in children generally less than 50 mg/day
- May be useful to monitor plasma levels in children and adolescents



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Crosses the placenta
- Should be used only if potential benefits outweigh potential risks
- Adverse effects have been reported in infants whose mothers took a TCA (lethargy, withdrawal symptoms, fetal malformations)
- Evaluate for treatment with an antidepressant with a better risk/benefit ratio

Breast Feeding

- Some drug is found in mother's breast milk
- ✖ Recommended either to discontinue drug or bottle feed
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients this may mean continuing treatment during breast feeding

- Underweight patients may be more susceptible to adverse cardiovascular effects
- Children, patients with inadequate hydration, and patients with cardiac disease may be more susceptible to TCA-induced cardiotoxicity than healthy adults
- For the expert only: although generally prohibited, a heroic but potentially dangerous treatment for severely treatment-resistant patients is for an expert to give a tricyclic/tetracyclic antidepressant other than clomipramine simultaneously with an MAOI for patients who fail to respond to numerous other antidepressants
- If this option is elected, start the MAOI with the tricyclic/tetracyclic antidepressant simultaneously at low doses after appropriate drug washout, then alternately increase doses of these agents every few days to a week as tolerated
- Although very strict dietary and concomitant drug restrictions must be observed to prevent hypertensive crises and serotonin syndrome, the most common side effects of MAOI and tricyclic/tetracyclic antidepressant combinations may be weight gain and orthostatic hypotension
- Patients on TCAs should be aware that they may experience symptoms such as photosensitivity or blue-green urine
- SSRIs may be more effective than TCAs in women, and TCAs may be more effective than SSRIs in men
- Not recommended for first-line use in children with ADHD because of the availability of safer treatments with better documented efficacy and because of nortriptyline's potential for sudden death in children

Pearls

- TCAs are often a first-line treatment option for chronic pain
- TCAs are no longer generally considered a first-line option for depression because of their side effect profile
- TCAs continue to be useful for severe or treatment-resistant depression
- Noradrenergic reuptake inhibitors such as nortriptyline can be used as a second-line treatment for smoking cessation, cocaine dependence, and attention deficit disorder
- TCAs may aggravate psychotic symptoms
- Alcohol should be avoided because of additive CNS effects

- Phenotypic testing may be necessary to detect this genetic variant prior to dosing with a tricyclic/tetracyclic antidepressant, especially in vulnerable populations such as children, elderly, cardiac populations, and those on concomitant medications
- Patients who seem to have extraordinarily severe side effects at normal or low doses

may have this phenotypic CYP450 2D6 variant and require low doses or switching to another antidepressant not metabolized by 2D6



Suggested Reading

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THERAPEUTICS

Brands

- Zyprexa
- Symbyax (olanzapine-fluoxetine combination)
- Relprevv

see index for additional brand names

Generic? Yes**Class**

- Neuroscience-based Nomenclature: dopamine and serotonin receptor antagonist (DS-RAn)
- Atypical antipsychotic (serotonin-dopamine antagonist; second-generation antipsychotic; also a mood stabilizer)

Commonly Prescribed for

(bold for FDA approved)

- **Schizophrenia (ages 13 and older)**
- Maintaining response in schizophrenia
- Acute agitation associated with schizophrenia (intramuscular)
- Acute mania/mixed mania (monotherapy and adjunct to lithium or valproate) (ages 13 and older)
- Bipolar maintenance
- Acute agitation associated with bipolar I mania (intramuscular)
- Bipolar depression [in combination with fluoxetine (**Symbyax**)]
- Treatment-resistant depression [in combination with fluoxetine (**Symbyax**)]
- Other psychotic disorders
- Behavioral disturbances in dementias
- Behavioral disturbances in children and adolescents
- Disorders associated with problems with impulse control
- Borderline personality disorder

**How the Drug Works**

- Blocks dopamine 2 receptors, reducing positive symptoms of psychosis and stabilizing affective symptoms
- Blocks serotonin 2A receptors, causing enhancement of dopamine release in certain brain regions and thus reducing motor side effects and possibly improving cognitive and affective symptoms

- Interactions at a myriad of other neurotransmitter receptors may contribute to olanzapine's efficacy

✳ Specifically, antagonist actions at 5HT2C receptors may contribute to efficacy for cognitive and affective symptoms in some patients

✳ 5HT2C antagonist actions plus serotonin reuptake blockade of fluoxetine add to the actions of olanzapine when given as Symbyax (olanzapine-fluoxetine combination)

How Long Until It Works

- Psychotic and manic symptoms can improve within 1 week, but it may take several weeks for full effect on behavior as well as on cognition and affective stabilization
- Classically recommended to wait at least 4–6 weeks to determine efficacy of drug, but in practice some patients require up to 16–20 weeks to show a good response, especially on cognitive symptoms
- IM formulation can reduce agitation in 15–30 minutes

If It Works

- Most often reduces positive symptoms in schizophrenia but does not eliminate them
- Can improve negative symptoms, as well as aggressive, cognitive, and affective symptoms in schizophrenia
- Most schizophrenic patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third
- Perhaps 5–15% of schizophrenic patients can experience an overall improvement of greater than 50–60%, especially when receiving stable treatment for more than a year
- Such patients are considered super-responders or "awakeners" since they may be well enough to be employed, live independently, and sustain long-term relationships
- Many bipolar patients may experience a reduction of symptoms by half or more
- Continue treatment until reaching a plateau of improvement
- After reaching a satisfactory plateau, continue treatment for at least a year after first episode of psychosis

- For second and subsequent episodes of psychosis, treatment may need to be indefinite
- Even for first episodes of psychosis, it may be preferable to continue treatment indefinitely to avoid subsequent episodes
- Treatment may not only reduce mania but also prevent recurrences of mania in bipolar disorder

If It Doesn't Work

- Try one of the other atypical antipsychotics (risperidone, quetiapine, ziprasidone, aripiprazole, paliperidone, amisulpride, asenapine, iloperidone, lurasidone)
- If 2 or more antipsychotic monotherapies do not work, consider clozapine
- Some patients may require treatment with a conventional antipsychotic
- If no first-line atypical antipsychotic is effective, consider higher doses or augmentation with valproate or lamotrigine
- Consider noncompliance and switch to another antipsychotic with fewer side effects or to an antipsychotic that can be given by depot injection
- Consider initiating rehabilitation and psychotherapy such as cognitive remediation
- Consider presence of concomitant drug abuse



Best Augmenting Combos for Partial Response or Treatment Resistance

- Valproic acid (valproate, divalproex, divalproex ER)
- Other mood-stabilizing anticonvulsants (carbamazepine, oxcarbazepine, lamotrigine)
- Lithium
- Benzodiazepines
- Fluoxetine and other antidepressants may be effective augmenting agents to olanzapine for bipolar depression, psychotic depression, and for unipolar depression not responsive to antidepressants alone (e.g., olanzapine-fluoxetine combination)

Tests

Before starting an atypical antipsychotic

- Weigh all patients and track BMI during treatment
- Get baseline personal and family history of diabetes, obesity, dyslipidemia, hypertension, and cardiovascular disease

• Get waist circumference (at umbilicus), blood pressure, fasting plasma glucose, and fasting lipid profile

- Determine if the patient is
 - overweight (BMI 25.0–29.9)
 - obese (BMI ≥ 30)
 - has pre-diabetes (fasting plasma glucose 100–125 mg/dL)
 - has diabetes (fasting plasma glucose >126 mg/dL)
 - has hypertension (BP $>140/90$ mm Hg)
 - has dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol)
- Treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management

Monitoring after starting an atypical antipsychotic

- BMI monthly for 3 months, then quarterly
- Consider monitoring fasting triglycerides monthly for several months in patients at high risk for metabolic complications and when initiating or switching antipsychotics
- Blood pressure, fasting plasma glucose, fasting lipids within 3 months and then annually, but earlier and more frequently for patients with diabetes or who have gained $>5\%$ of initial weight
- Treat or refer for treatment and consider switching to another atypical antipsychotic for patients who become overweight, obese, pre-diabetic, diabetic, hypertensive, or dyslipidemic while receiving an atypical antipsychotic
- Even in patients without known diabetes, be vigilant for the rare but life-threatening onset of diabetic ketoacidosis, which always requires immediate treatment, by monitoring for the rapid onset of polyuria, polydipsia, weight loss, nausea, vomiting, dehydration, rapid respiration, weakness, and clouding of sensorium, even coma
- Patients with liver disease should have blood tests a few times a year
- Patients with low white blood cell count (WBC) or history of drug-induced leucopenia/neutropenia should have complete blood count (CBC) monitored frequently during the first few months and olanzapine should be discontinued at the first sign of decline of WBC in the absence of other causative factors

SIDE EFFECTS

How Drug Causes Side Effects

- By blocking histamine 1 receptors in the brain, it can cause sedation and possibly weight gain
- By blocking alpha 1 adrenergic receptors, it can cause dizziness, sedation, and hypotension
- By blocking muscarinic 1 receptors, it can cause dry mouth, constipation, and sedation
- By blocking dopamine 2 receptors in the striatum, it can cause motor side effects (unusual)
- Mechanism of weight gain and increased incidence of diabetes and dyslipidemia with atypical antipsychotics is unknown but insulin regulation may be impaired by blocking pancreatic M3 muscarinic receptors

Notable Side Effects

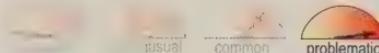
- Probably increases risk for diabetes mellitus and dyslipidemia
- Dizziness, sedation
- Dry mouth, constipation, dyspepsia, weight gain
- Peripheral edema
- Joint pain, back pain, chest pain, extremity pain, abnormal gait, ecchymosis
- Tachycardia
- Orthostatic hypotension, usually during initial dose titration
- Rare tardive dyskinesia (much reduced risk compared to conventional antipsychotics)
- Rare rash on exposure to sunlight



Life-Threatening or Dangerous Side Effects

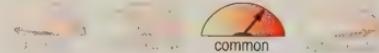
- Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking atypical antipsychotics
- Rare but serious skin condition known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
- Rare neuroleptic malignant syndrome (much reduced risk compared to conventional antipsychotics)
- Rare seizures
- Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis

Weight Gain



- Frequent and can be significant in amount
- Can become a health problem in some
- More than for some other antipsychotics, but never say always as not a problem in everyone

Sedation



- Many patients experience and/or can be significant in amount
- Usually transient
- May be less than for some antipsychotics, more than for others

What to Do About Side Effects

- Wait
- Wait
- Wait
- Take at bedtime to help reduce daytime sedation
- Anticholinergics may reduce motor side effects such as akathisia when present, but rarely necessary
- Weight loss, exercise programs, and medical management for high BMIs, diabetes, dyslipidemia
- Switch to another atypical antipsychotic

Best Augmenting Agents for Side Effects

- Benztrapine or trihexyphenidyl for motor side effects
- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 10–20 mg/day (oral or intramuscular)
- 6–12 mg olanzapine/25–50 mg fluoxetine (olanzapine-fluoxetine combination)
- 150–300 mg/2 weeks or 300–405 mg/4 weeks (see Olanzapine Pamoate after Pearls for dosing and use)

Dosage Forms

- Tablets 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg
- Orally disintegrating tablets 5 mg, 10 mg, 15 mg, 20 mg

- Intramuscular formulation 5 mg/mL, each vial contains 10 mg (available in some countries)
- Depot 210 mg, 300 mg, 405 mg
- Olanzapine-fluoxetine combination capsule (mg equivalent olanzapine/mg equivalent fluoxetine) 6 mg/25 mg, 6 mg/50 mg, 12 mg/25 mg, 12 mg/50 mg

How to Dose

- Initial 5–10 mg once daily orally; increase by 5 mg/day once a week until desired efficacy is reached; maximum approved dose is 20 mg/day
- For intramuscular formulation, recommended initial dose 10 mg; second injection of 5–10 mg may be administered 2 hours after first injection; maximum daily dose of olanzapine is 20 mg, with no more than 3 injections per 24 hours
- For olanzapine-fluoxetine combination, recommended initial dose 6 mg/25 mg once daily in evening; increase dose based on efficacy and tolerability; maximum generally 18 mg/75 mg



Dosing Tips – Oral

- **More may be more:** raising usual dose above 15 mg/day can be useful for acutely ill and agitated patients and some treatment-resistant patients, gaining efficacy without many more side effects
- Some heroic uses for patients who do not respond to other antipsychotics can occasionally justify dosing over 30 mg/day and short-term up to 90 mg/day
 - For high doses in treatment-resistant or violent patients, monitor therapeutic drug levels and target generally higher than the usual range of 5–75 mg/mL (i.e., greater than 125 mg/mL), but keep below the toxic range associated with QTc prolongation (700–800 mg/mL)
 - See also the Switching section, after Pearls, for initiating both oral and long-acting injectable
 - Rather than raise the dose above these levels in acutely agitated patients requiring acute antipsychotic actions, consider augmentation with a benzodiazepine or conventional antipsychotic, either orally or intramuscularly
 - Rather than raise the dose above these levels in partial responders, consider augmentation

with a mood-stabilizing anticonvulsant, such as valproate or lamotrigine

- Clearance of olanzapine is slightly reduced in women compared to men, so women may need lower doses than men
 - Children and elderly should generally be dosed at the lower end of the dosage spectrum
- Olanzapine intramuscularly can be given short-term, both to initiate dosing with oral olanzapine or another oral antipsychotic and to treat breakthrough agitation in patients maintained on oral antipsychotics
- Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³

Overdose

- Rarely lethal in monotherapy overdose; sedation, slurred speech

Long-Term Use

- Approved to maintain response in long-term treatment of schizophrenia
- Approved for long-term maintenance in bipolar disorder
- Often used for long-term maintenance in various behavioral disorders

Habit Forming

- No

How to Stop

- See Switching section of individual agents for how to stop olanzapine
- Rapid oral discontinuation may lead to rebound psychosis and worsening of symptoms

Pharmacokinetics

- Metabolites are inactive
- Parent drug has 21–54 hour half-life
- Substrate for CYP450 1A2 and 2D6
- Food does not affect absorption



Drug Interactions

- May increase effect of antihypertensive agents
- May antagonize levodopa, dopamine agonists
- Dose may need to be lowered if given with CYP450 1A2 inhibitors (e.g., fluvoxamine); raised if given in conjunction with CYP450 1A2 inducers (e.g., cigarette smoke, carbamazepine)



Other Warnings/ Precautions

- Olanzapine is associated with a rare but serious skin condition known as Drug Reaction with Eosinophilia (DRESS). DRESS may begin as a rash but can progress to other parts of the body and can include symptoms such as fever, swollen lymph nodes, swollen face, inflammation of organs, and an increase in white blood cells known as eosinophilia. In some cases, DRESS can lead to death. Clinicians prescribing olanzapine should inform patients about the risk of DRESS; patients who develop a fever with rash and swollen lymph nodes or swollen face should seek medical care. Patients are not advised to stop their medication without consulting their prescribing clinician.
- Use with caution in patients with conditions that predispose to hypotension (dehydration, overheating)
- Use with caution in patients with prostatic hypertrophy, angle-closure glaucoma, paralytic ileus
- Patients receiving the intramuscular formulation of olanzapine should be observed closely for hypotension
- Intramuscular formulation is not generally recommended to be administered with parenteral benzodiazepines; if patient requires a parenteral benzodiazepine it should be given at least 1 hour after intramuscular olanzapine
- Olanzapine should be used cautiously in patients at risk for aspiration pneumonia, as dysphagia has been reported

Do Not Use

- If there is a known risk of angle-closure glaucoma (intramuscular formulation)
- If patient has unstable medical condition (e.g., acute myocardial infarction, unstable angina pectoris, severe hypotension and/or bradycardia, sick sinus syndrome, recent heart surgery) (intramuscular formulation)
- If there is a proven allergy to olanzapine

SPECIAL POPULATIONS

Renal Impairment

- No dose adjustment required for oral formulation
- Not removed by hemodialysis
- For intramuscular formulation, consider lower starting dose (5 mg)

Hepatic Impairment

- May need to lower dose
- Patients with liver disease should have liver function tests a few times a year
- For moderate to severe hepatic impairment, starting oral dose 5 mg; increase with caution
- For intramuscular formulation, consider lower starting dose (5 mg)

Cardiac Impairment

- Drug should be used with caution because of risk of orthostatic hypotension

Elderly

- Some patients may tolerate lower doses better
- Increased incidence of stroke
- For intramuscular formulation, recommended starting dose is 2.5–5 mg; a second injection of 2.5–5 mg may be administered 2 hours after first injection; no more than 3 injections should be administered within 24 hours
- Although atypical antipsychotics are commonly used for behavioral disturbances in dementia, no agent has been approved for treatment of elderly patients with dementia-related psychosis
- Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo, and also have an increased risk of cerebrovascular events



Children and Adolescents

- Approved for use in schizophrenia and manic/mixed episodes (ages 13 and older for both)
- Clinical experience and early data suggest olanzapine is probably safe and effective for behavioral disturbances in children and adolescents

- Children and adolescents using olanzapine may need to be monitored more often than adults
- Intramuscular formulation has not been studied in patients under 18 and is not recommended for use in this population



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- There is a risk of abnormal muscle movements and withdrawal symptoms in newborns whose mothers took an antipsychotic during the third trimester; symptoms may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty feeding
- Psychotic symptoms may worsen during pregnancy, and some form of treatment may be necessary
- Early findings of infants exposed to olanzapine in utero currently do not show adverse consequences
- Olanzapine may be preferable to anticonvulsant mood stabilizers if treatment is required during pregnancy
- National Pregnancy Registry for Atypical Antipsychotics: 1-866-961-2388 or <http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/>

Breast Feeding

- Unknown if olanzapine is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- Recommended either to discontinue drug or bottle feed
- Infants of women who choose to breast feed while on olanzapine should be monitored for possible adverse effects

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Some cases of psychosis and bipolar disorder refractory to treatment with other antipsychotics
- Often a preferred augmenting agent in bipolar depression or treatment-resistant unipolar depression
- Patients needing rapid onset of antipsychotic action without drug titration
- Patients switching from intramuscular olanzapine to an oral preparation

Potential Disadvantages

- Patients concerned about gaining weight
- Patients with diabetes mellitus, obesity, and/or dyslipidemia

Primary Target Symptoms

- Positive symptoms of psychosis
- Negative symptoms of psychosis
- Cognitive symptoms
- Unstable mood (both depressed mood and mania)
- Aggressive symptoms



Pearls

- Recent landmark head-to-head study in schizophrenia suggests greater effectiveness (i.e., lower dropouts of all causes) at moderately high doses compared to some other atypical and conventional antipsychotics at moderate doses
- Same recent head-to-head study in schizophrenia suggests greater efficacy but greater metabolic side effects compared to some other atypical and conventional antipsychotics
- Well accepted for use in schizophrenia and bipolar disorder, including difficult cases
- Documented utility in treatment-refractory cases, especially at higher doses
- Documented efficacy as augmenting agent to SSRIs (fluoxetine) in nonpsychotic treatment-resistant major depressive disorder
- Documented efficacy in bipolar depression, especially in combination with fluoxetine
- More weight gain than many other antipsychotics – does not mean every patient gains weight
- Motor side effects unusual at low- to mid-doses
- Less sedation than for some other antipsychotics, more than for others

- Controversial as to whether olanzapine has more risk of diabetes and dyslipidemia than other antipsychotics
- Cigarette smoke can decrease olanzapine levels and patients may require a dose increase if they begin or increase smoking
- A short-acting intramuscular dosage formulation is available
- Long-acting intramuscular dosage formulation is also approved
- Patients with inadequate responses to atypical antipsychotics may benefit from determination of plasma drug levels and, if low, a dosage increase even beyond the usual prescribing limits
- Patients with inadequate responses to atypical antipsychotics may also benefit from a trial of augmentation with a conventional antipsychotic or switching to a conventional antipsychotic
- However, long-term polypharmacy with a combination of a conventional antipsychotic with an atypical antipsychotic may combine their side effects without clearly augmenting the efficacy of either
- For treatment-resistant patients, especially those with impulsivity, aggression, violence, and self-harm, long-term polypharmacy with 2 atypical antipsychotics or with 1 atypical antipsychotic and 1 conventional antipsychotic may be useful or even necessary while closely monitoring
- In such cases, it may be beneficial to combine 1 depot antipsychotic with 1 oral antipsychotic
- Although a frequent practice by some prescribers, adding 2 conventional antipsychotics together has little rationale and may reduce tolerability without clearly enhancing efficacy

PAMOATE

Needle gauge	19
Dosage forms	210 mg, 300 mg, 405 mg
Injection volume	150 mg/mL (range 1.0–2.7 mL)

Usual Dosage Range

- 150–300 mg/2 weeks or 300–405 mg/4 weeks

How to Dose

- Conversion from oral: dose should be loaded during the initial 8 weeks based on the prior stable oral dose of olanzapine

Daily oral olanzapine dose	LAI dose: first 8 weeks	LAI dose: after 8 weeks
10 mg	210 mg/2 weeks OR 405 mg/4 weeks	150 mg/2 weeks OR 300 mg/4 weeks
15 mg	300 mg/2 weeks	210 mg/2 weeks OR 405 mg/4 weeks
20 mg	300 mg/2 weeks	300 mg/2 weeks

- Oral supplementation may be needed if adequate loading is not used
- Maximum dose 300 mg/2 weeks

Dosing Tips

- With LAIs, the absorption rate constant is slower than the elimination rate constant, thus resulting in “flip-flop” kinetics—i.e., time to steady-state is a function of absorption rate, while concentration at steady-state is a function of elimination rate
- The rate-limiting step for plasma drug levels for LAIs is not drug metabolism, but rather slow absorption from the injection site
- In general, 5 half-lives of any medication are needed to achieve 97% of steady-state levels
- The long half-lives of depot antipsychotics mean that one must either adequately load the dose (if possible) or provide oral supplementation
- The failure to adequately load the dose leads either to prolonged cross-titration

Vehicle	Water
Tmax	3–4 days
T1/2 with multiple dosing	30 days
Time to reach steady state	3 months
Able to be loaded	Yes
Dosing schedule (maintenance)	2 weeks or 4 weeks
Injection site	Intramuscular gluteal

OLANZAPINE (continued)

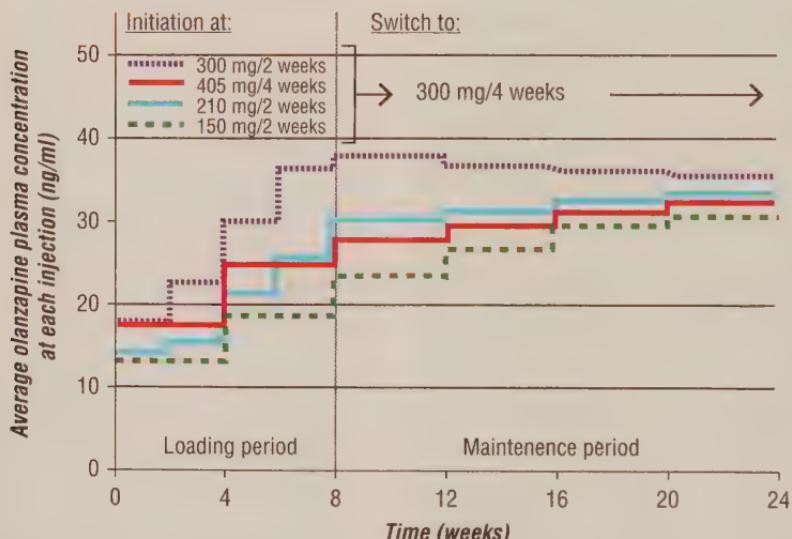
from oral antipsychotic or to sub-therapeutic antipsychotic plasma levels for weeks or months in patients who are not receiving (or adhering to) oral supplementation

- Because plasma antipsychotic levels increase gradually over time, dose requirements may ultimately decrease from initial; obtaining periodic plasma levels can be beneficial to prevent unnecessary plasma level creep

- The time to get a blood level for patients receiving LAI is the morning of the day they will receive their next injection
- Advantages: efficacy advantage of oral olanzapine
- Disadvantages: 3-hour post-injection monitoring required due to risk (0.2%) of post-injection delirium from vascular breach
- Response threshold is generally 21 ng/mL; plasma levels greater than 176 ng/mL are generally not well tolerated

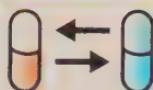
SWITCHING FROM ORAL ANTIPSYCHOTICS TO OLANZAPINE PAMOATE

Expected Olanzapine Levels Without Oral Coverage



- Discontinuation of oral antipsychotic can begin immediately if adequate loading is pursued
- How to discontinue oral formulations
 - Down-titration is not required for: amisulpride, aripiprazole, brexpiprazole, cariprazine, olanzapine, paliperidone ER
 - 1-week down-titration is required for: iloperidone, lurasidone, risperidone, ziprasidone, asenapine, quetiapine
 - 4+ week down-titration may be required for: clozapine

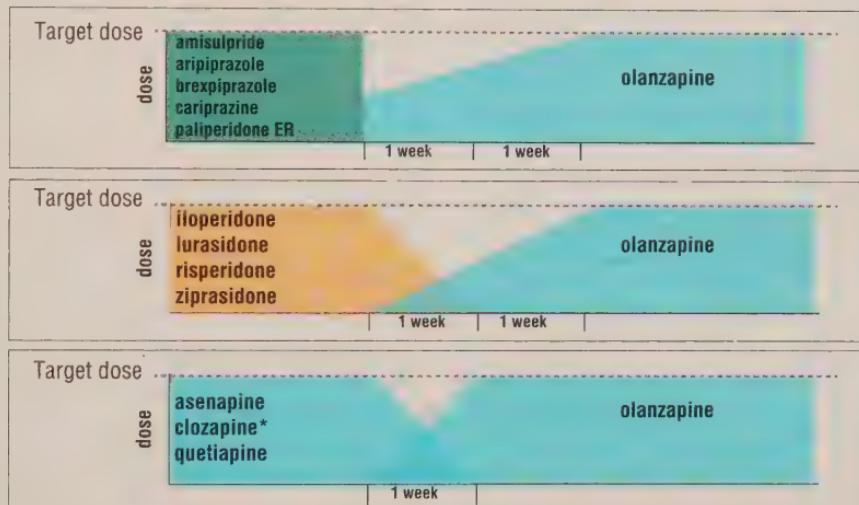
THE ART OF SWITCHING



Switching from Oral Antipsychotics to Oral Olanzapine

- With aripiprazole, amisulpride, and paliperidone ER, immediate stop is possible; begin olanzapine at middle dose
- With risperidone, ziprasidone, iloperidone, and lurasidone, begin olanzapine gradually, titrating over at least 2 weeks to allow patients to become tolerant to the sedating effect

*May need to taper clozapine slowly over 4 weeks or longer



Suggested Reading

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THERAPEUTICS

Brands

- Paxil

- Paxil CR

see index for additional brand names

Generic? Yes**Class**

- Neuroscience-based Nomenclature: serotonin reuptake inhibitor (S-RI)
- SSRI (selective serotonin reuptake inhibitor); often classified as an antidepressant, but it is not just an antidepressant

Commonly Prescribed for

(bold for FDA approved)

- Major depressive disorder (paroxetine and paroxetine CR)**
- Obsessive-compulsive disorder (OCD)**
- Panic disorder (paroxetine and paroxetine CR)**
- Social anxiety disorder (social phobia) (paroxetine and paroxetine CR)**
- Posttraumatic stress disorder (PTSD)**
- Generalized anxiety disorder (GAD)**
- Premenstrual dysphoric disorder (PMDD) (paroxetine CR)**
- Vasomotor symptoms (Brisdelle)**

**How the Drug Works**

- Boosts neurotransmitter serotonin
- Blocks serotonin reuptake pump (serotonin transporter)
- Desensitizes serotonin receptors, especially serotonin 1A autoreceptors
- Presumably increases serotonergic neurotransmission
- Paroxetine also has mild anticholinergic actions
- Paroxetine may have mild norepinephrine reuptake blocking actions

How Long Until It Works

* Some patients may experience relief of insomnia or anxiety early after initiation of treatment

- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all

- By contrast, for generalized anxiety, onset of response and increases in remission rates may still occur after 8 weeks of treatment and for up to 6 months after initiating dosing
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Continue treatment until all symptoms are gone (remission) or significantly reduced (e.g., OCD, PTSD)
- Once symptoms are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders may also need to be indefinite

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating in depression)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some patients who have an initial response may relapse even though they continue treatment, sometimes called "poop-out"
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer

**Best Augmenting Combos for Partial Response or Treatment Resistance**

- Trazodone, especially for insomnia
- Bupropion, mirtazapine, reboxetine, or atomoxetine (add with caution and at lower

PAROXETINE (continued)

doses since paroxetine could theoretically raise atomoxetine levels); use combinations of antidepressants with caution as this may activate bipolar disorder and suicidal ideation

- Modafinil, especially for fatigue, sleepiness, and lack of concentration
- Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression, treatment-resistant depression, or treatment-resistant anxiety disorders
- Benzodiazepines
- If all else fails for anxiety disorders, consider gabapentin or tiagabine
- Hypnotics for insomnia
- Classically, lithium, buspirone, or thyroid hormone

Tests

- None for healthy individuals

SIDE EFFECTS

How Drug Causes Side Effects

- Theoretically due to increases in serotonin concentrations at serotonin receptors in parts of the brain and body other than those that cause therapeutic actions (e.g., unwanted actions of serotonin in sleep centers causing insomnia, unwanted actions of serotonin in the gut causing diarrhea, etc.)
- Increasing serotonin can cause diminished dopamine release and might contribute to emotional flattening, cognitive slowing, and apathy in some patients
- Most side effects are immediate but often go away with time, in contrast to most therapeutic effects, which are delayed and are enhanced over time

★ Paroxetine's weak antimuscarinic properties can cause constipation, dry mouth, sedation

Notable Side Effects

- Sexual dysfunction (dose-dependent; men: delayed ejaculation, erectile dysfunction; men and women: decreased sexual desire, anorgasmia)
- Gastrointestinal (decreased appetite, nausea, diarrhea, constipation, dry mouth)
- Mostly CNS (insomnia but also sedation, agitation, dose-dependent tremors, headache, dizziness)

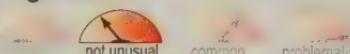
- Weight gain
- Activation (short-term; patients with diagnosed or undiagnosed bipolar or psychotic disorders may be more vulnerable to CNS-activating actions of SSRIs)
- Autonomic (dose-dependent sweating)
- Bruising and rare bleeding
- SIADH (syndrome of inappropriate antiidiuretic hormone secretion)



Life-Threatening or Dangerous Side Effects

- Rare seizures
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Occurs in significant minority

Sedation



- Many experience and/or can be significant in amount
- Generally transient

What to Do About Side Effects

- Wait
- Wait
- Wait
- If paroxetine is sedating, take at night to reduce daytime drowsiness
- Reduce dose to 5–10 mg (12.5 mg for CR) until side effects abate, then increase as tolerated, usually to at least 20 mg (25 mg CR)
- In a few weeks, switch or add other drugs

Best Augmenting Agents for Side Effects

- Often best to try another SSRI or another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
- Trazodone or a hypnotic for insomnia
- Bupropion, sildenafil, vardenafil, or tadalafil for sexual dysfunction

- Bupropion for emotional flattening, cognitive slowing, or apathy
- Mirtazapine for insomnia, agitation, and gastrointestinal side effects
- Benzodiazepines for jitteriness and anxiety, especially at initiation of treatment and especially for anxious patients
- Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of paroxetine

DOSING AND USE

Usual Dosage Range

- Depression: 20–50 mg (25–62.5 mg CR)
- Vasomotor symptoms: 7.5 mg at bedtime

Dosage Forms

- Tablets 10 mg scored, 20 mg scored, 30 mg, 40 mg
- Controlled-release tablets 12.5 mg, 25 mg
- Liquid 10 mg/5mL – 250 mL bottle

How to Dose

- Depression: initial 20 mg (25 mg CR); usually wait a few weeks to assess drug effects before increasing dose, but can increase by 10 mg/day (12.5 mg/day CR) once a week; maximum generally 50 mg/day (62.5 mg/day CR); single dose
- Panic disorder: initial 10 mg/day (12.5 mg/day CR); usually wait a few weeks to assess drug effects before increasing dose, but can increase by 10 mg/day (12.5 mg/day CR) once a week; maximum generally 60 mg/day (75 mg/day CR); single dose
- Social anxiety disorder: initial 20 mg/day (25 mg/day CR); usually wait a few weeks to assess drug effects before increasing dose, but can increase by 10 mg/day

(12.5 mg/day CR) once a week; maximum 60 mg/day (75 mg/day CR); single dose

- Other anxiety disorders: initial 20 mg/day (25 mg/day CR); usually wait a few weeks to assess drug effects before increasing dose, but can increase by 10 mg/day (12.5 mg/day CR) once a week; maximum 60 mg/day (75 mg/day CR); single dose



Dosing Tips

- 20-mg tablet is scored, so to save costs, give 10 mg as half of 20-mg tablet, since 10-mg and 20-mg tablets cost about the same in many markets
 - Given once daily, often at bedtime, but any time of day tolerated
 - 20 mg/day (25 mg/day CR) is often sufficient for patients with social anxiety disorder and depression
 - Other anxiety disorders, as well as difficult cases in general, may require higher dosing
 - Occasional patients are dosed above 60 mg/day (75 mg/day CR), but this is for experts and requires caution
 - If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar disorder and switch to a mood stabilizer or an atypical antipsychotic
 - Liquid formulation easiest for doses below 10 mg when used for cases that are very intolerant to paroxetine or especially for very slow down-titration during discontinuation for patients with withdrawal symptoms
 - Paroxetine CR tablets not scored, so chewing or cutting in half can destroy controlled-release properties
 - Unlike other SSRIs and antidepressants where dosage increments can be double and triple the starting dose, paroxetine's dosing increments are in 50% increments (i.e., 20, 30, 40; or 25, 37.5, 50 CR)
 - Paroxetine inhibits its own metabolism and thus plasma concentrations can double when oral doses increase by 50%; plasma concentrations can increase 2–7-fold when oral doses are doubled
- * Main advantage of CR is reduced side effects, especially nausea and perhaps sedation, sexual dysfunction, and withdrawal

PAROXETINE (continued)

- ✿ For patients with severe problems discontinuing paroxetine, dosing may need to be tapered over many months (i.e., reduce dose by 1% every 3 days by crushing tablet and suspending or dissolving in 100 mL of fruit juice and then disposing of 1 mL while drinking the rest; 3–7 days later, dispose of 2 mL, and so on). This is both a form of very slow biological tapering and a form of behavioral desensitization (not for CR)
- For some patients with severe problems discontinuing paroxetine, it may be useful to add an SSRI with a long half-life, especially fluoxetine, prior to taper of paroxetine; while maintaining fluoxetine dosing, first slowly taper paroxetine and then taper fluoxetine
- Be sure to differentiate between reemergence of symptoms requiring reinstitution of treatment and withdrawal symptoms

Overdose

- Rarely lethal in monotherapy overdose; vomiting, sedation, heart rhythm disturbances, dilated pupils, dry mouth

Long-Term Use

- Safe

Habit Forming

- No

How to Stop

- Taper to avoid withdrawal effects (dizziness, nausea, stomach cramps, sweating, tingling, dysesthesias)
- Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation
- If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly
- ✿ Withdrawal effects can be more common or more severe with paroxetine than with some other SSRIs
- Paroxetine's withdrawal effects may be related in part to the fact that it inhibits its own metabolism
- Thus, when paroxetine is withdrawn, the rate of its decline can be faster as it stops inhibiting its metabolism

- Controlled-release paroxetine may slow the rate of decline and thus reduce withdrawal reactions in some patients
- Readaptation of cholinergic receptors after prolonged blockade may contribute to withdrawal effects of paroxetine

Pharmacokinetics

- Inactive metabolites
- Half-life approximately 24 hours
- Inhibits CYP450 2D6



Drug Interactions

- Tramadol increases the risk of seizures in patients taking an antidepressant
- Can increase TCA levels; use with caution with TCAs or when switching from a TCA to paroxetine
- Can cause a fatal "serotonin syndrome" when combined with MAOIs, so do not use with MAOIs or for at least 14 days after MAOIs are stopped
- Do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing paroxetine
- May displace highly protein bound drugs (e.g., warfarin)
- There are reports of elevated theophylline levels associated with paroxetine treatment, so it is recommended that theophylline levels be monitored when these drugs are administered together
- May increase anticholinergic effects of procyclidine and other drugs with anticholinergic properties
- Can rarely cause weakness, hyperreflexia, and incoordination when combined with sumatriptan or possibly with other triptans, requiring careful monitoring of patient
- Possible increased risk of bleeding, especially when combined with anticoagulants (e.g., warfarin, NSAIDs)
- NSAIDs may impair effectiveness of SSRIs
- Via CYP450 2D6 inhibition, paroxetine could theoretically interfere with the analgesic actions of codeine, and increase the plasma levels of some beta blockers and of atomoxetine
- Via CYP450 2D6 inhibition, paroxetine could theoretically increase concentrations of thioridazine and cause dangerous cardiac arrhythmias

- Paroxetine increases pimozide levels, and pimozide prolongs QT interval, so concomitant use of pimozide and paroxetine is contraindicated



Other Warnings/ Precautions

- Add or initiate other antidepressants with caution for up to 2 weeks after discontinuing paroxetine
- Use with caution in patients with history of seizures
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is taking an MAOI
- If patient is taking thioridazine
- If patient is taking pimozide
- If patient is taking tamoxifen
- If there is a proven allergy to paroxetine

SPECIAL POPULATIONS

Renal Impairment

- Lower dose [initial 10 mg/day (12.5 mg CR), maximum 40 mg/day (50 mg/day CR)]

Hepatic Impairment

- Lower dose [initial 10 mg/day (12.5 mg CR), maximum 40 mg/day (50 mg/day CR)]

Cardiac Impairment

- Preliminary research suggests that paroxetine is safe in these patients
- Treating depression with SSRIs in patients with acute angina or following myocardial

infarction may reduce cardiac events and improve survival as well as mood

Elderly

- Lower dose [initial 10 mg/day (12.5 mg CR), maximum 40 mg/day (50 mg/day CR)]
- Risk of SIADH with SSRIs is higher in the elderly
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Not specifically approved, but preliminary evidence suggests efficacy in children and adolescents with OCD, social phobia, or depression



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLL or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Not generally recommended for use during pregnancy, especially during first trimester
- Epidemiological data have shown an increased risk of cardiovascular malformations (primarily ventricular and atrial septal defects) in infants born to women who took paroxetine during the first trimester (absolute risk is small)

PAROXETINE (continued)

- Unless the benefits of paroxetine to the mother justify continuing treatment, consider discontinuing paroxetine or switching to another antidepressant
- Paroxetine use late in pregnancy may be associated with higher risk of neonatal complications, including respiratory distress
- At delivery there may be more bleeding in the mother and transient irritability or sedation in the newborn
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy
- SSRI use beyond the 20th week of pregnancy may be associated with increased risk of pulmonary hypertension in newborns, although this is not proven
- Exposure to SSRIs late in pregnancy may be associated with increased risk of gestational hypertension and preeclampsia
- Neonates exposed to SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding; reported symptoms are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome, and include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying

Breast Feeding

- Some drug is found in mother's breast milk
- Trace amounts may be present in nursing children whose mothers are on paroxetine
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period

- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients, this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients with anxiety disorders and insomnia
- Patients with mixed anxiety/depression

Potential Disadvantages

- Patients with hypersomnia
- Alzheimer/cognitive disorders
- Patients with psychomotor retardation, fatigue, and low energy

Primary Target Symptoms

- Depressed mood
- Anxiety
- Sleep disturbance, especially insomnia
- Panic attacks, avoidant behavior, re-experiencing, hyperarousal



Pearls

- ✿ Often a preferred treatment of anxious depression as well as major depressive disorder comorbid with anxiety disorders
- ✿ Withdrawal effects may be more likely than for some other SSRIs when discontinued (especially akathisia, restlessness, gastrointestinal symptoms, dizziness, tingling, dysesthesias, nausea, stomach cramps, restlessness)
- Inhibits own metabolism, so dosing is not linear
- ✿ Paroxetine has mild anticholinergic actions that can enhance the rapid onset of anxiolytic and hypnotic efficacy but also cause mild anticholinergic side effects
- Can cause cognitive and affective "flattening"
- May be less activating than other SSRIs
- Paroxetine is a potent CYP450 2D6 inhibitor
- SSRIs may be less effective in women over 50, especially if they are not taking estrogen

- SSRIs may be useful for hot flushes in perimenopausal women
- Some anecdotal reports suggest greater weight gain and sexual dysfunction than some other SSRIs, but the clinical significance of this is unknown
- For sexual dysfunction, can augment with bupropion, sildenafil, tadalafil, or switch to a non-SSRI such as bupropion or mirtazapine
- Some postmenopausal women's depression will respond better to

- paroxetine plus estrogen augmentation than to paroxetine alone
- Nonresponse to paroxetine in elderly may require consideration of mild cognitive impairment or Alzheimer disease
- CR formulation may enhance tolerability, especially for nausea
- Can be better tolerated than some SSRIs for patients with anxiety and insomnia and can reduce these symptoms early in dosing



Suggested Reading

- Bourin M, Chue P, Guillon Y. Paroxetine: a review. *CNS Drug Rev* 2001;7:25–47.
- Gibiino S, Serretti A. Paroxetine for the treatment of depression: a critical update. *Expert Opin Pharmacother* 2012;13(3):421–31.
- Green B. Focus on paroxetine. *Curr Med Res Opin* 2003;19:13–21.

Wagstaff AJ, Cheer SM, Matheson AJ, Ormrod D, Goa KL. Paroxetine: an update of its use in psychiatric disorders in adults. *Drugs* 2002;62:655–703.

THERAPEUTICS

Brands

- Nardil
- Nardelzine

see index for additional brand names

Generic? Yes**Class**

- Neuroscience-based Nomenclature: serotonin, norepinephrine, dopamine enzyme inhibitor (SN-EI)
- Monoamine oxidase inhibitor (MAOI)

Commonly Prescribed for

(bold for FDA approved)

- Depressed patients characterized as “atypical,” “nonendogenous,” or “neurotic”
- Treatment-resistant depression
- Treatment-resistant panic disorder
- Treatment-resistant social anxiety disorder

**How the Drug Works**

- Irreversibly blocks monoamine oxidase (MAO) from breaking down norepinephrine, serotonin, and dopamine
- This presumably boosts noradrenergic, serotonergic, and dopaminergic neurotransmission

How Long Until It Works

- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Continue treatment until all symptoms are gone (remission)
- Once symptoms gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite

- Use in anxiety disorders may also need to be indefinite

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some patients who have an initial response may relapse even though they continue treatment, sometimes called “poop-out”
- Consider increasing dose, switching to another agent, or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer

Best Augmenting Combos for Partial Response or Treatment Resistance

- Augmentation of MAOIs has not been systematically studied, and this is something for the expert, to be done with caution and with careful monitoring
- A stimulant such as d-amphetamine or methylphenidate (with caution; may activate bipolar disorder and suicidal ideation; may elevate blood pressure)
- Lithium
- Mood-stabilizing anticonvulsants
- Atypical antipsychotics (with special caution for those agents with monoamine reuptake blocking properties, such as ziprasidone and zotepine)

Tests

- Patients should be monitored for changes in blood pressure
- Patients receiving high doses or long-term treatment should have hepatic function evaluated periodically
- Since MAOIs are frequently associated with weight gain, before starting treatment, weigh all patients and determine if

PHENELZINE (continued)

the patient is already overweight (BMI 25.0–29.9) or obese (BMI ≥30)

- Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–125 mg/dL), diabetes (fasting plasma glucose >126 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management

- Monitor weight and BMI during treatment
- While giving a drug to a patient who has gained >5% of initial weight, consider evaluating for the presence of pre-diabetes, diabetes, or dyslipidemia, or consider switching to a different antidepressant

SIDE EFFECTS

How Drug Causes Side Effects

- Theoretically due to increases in monoamines in parts of the brain and body and at receptors other than those that cause therapeutic actions (e.g., unwanted actions of serotonin in sleep centers causing insomnia, unwanted actions of norepinephrine on vascular smooth muscle causing changes in blood pressure, etc.)
- Side effects are generally immediate, but immediate side effects often disappear in time

Notable Side Effects

- Dizziness, sedation, headache, sleep disturbances, fatigue, weakness, tremor, movement problems, blurred vision, increased sweating
- Constipation, dry mouth, nausea, change in appetite, weight gain
- Sexual dysfunction
- Orthostatic hypotension (dose-related); syncope may develop at high doses



Life-Threatening or Dangerous Side Effects

- Hypertensive crisis (especially when MAOIs are used with certain tyramine-containing foods or prohibited drugs)

- Induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)
- Seizures
- Hepatotoxicity

Weight Gain



- Many experience and/or can be significant in amount

Sedation



- Many experience and/or can be significant in amount
- Can also cause activation

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- Take at night if daytime sedation
- Switch after appropriate washout to an SSRI or newer antidepressant

Best Augmenting Agents for Side Effects

- Trazodone (with caution) for insomnia
- Benzodiazepines for insomnia
- Single oral or sublingual dose of a calcium channel-blocker (e.g., nifedipine) for urgent treatment of hypertension due to drug interaction or dietary tyramine
- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 45–75 mg/day

Dosage Forms

- Tablet 15 mg

How to Dose

- Initial 45 mg/day in 3 divided doses; increase to 60–90 mg/day; after desired therapeutic effect is achieved lower dose as far as possible



Dosing Tips

- Once dosing is stabilized, some patients may tolerate once or twice daily dosing rather than 3-times-a-day dosing
- Orthostatic hypotension, especially at high doses, may require splitting into 4 daily doses
- Patients receiving high doses may need to be evaluated periodically for effects on the liver
- Little evidence to support efficacy of phenelzine below doses of 45 mg/day

Overdose

- Death may occur; dizziness, ataxia, sedation, headache, insomnia, restlessness, anxiety, irritability, cardiovascular effects, confusion, respiratory depression, coma

Long-Term Use

- May require periodic evaluation of hepatic function
- MAOIs may lose efficacy long-term

Habit Forming

- Some patients have developed dependence to MAOIs

How to Stop

- Generally no need to taper, as the drug wears off slowly over 2–3 weeks

Pharmacokinetics

- Clinical duration of action may be up to 14 days due to irreversible enzyme inhibition



Drug Interactions

- Tramadol may increase the risk of seizures in patients taking an MAOI
- Can cause a fatal “serotonin syndrome” when combined with drugs that block serotonin reuptake, so do not use with a serotonin reuptake inhibitor or for 5 half-lives after stopping the serotonin reuptake inhibitor (see Table 1 after Pearls)
- Hypertensive crisis with headache, intracranial bleeding, and death may result from combining MAOIs with sympathomimetic drugs (e.g., amphetamines, methylphenidate, cocaine, dopamine, epinephrine, norepinephrine, and

related compounds methyldopa, levodopa, L-tryptophan, L-tyrosine, and phenylalanine)

- Do not combine with another MAOI, alcohol, or guanethidine
- Adverse drug reactions can result from combining MAOIs with tricyclic/tetracyclic antidepressants and related compounds, including carbamazepine, cyclobenzaprine, and mirtazapine, and should be avoided except by experts to treat difficult cases
- MAOIs in combination with spinal anesthesia may cause combined hypotensive effects
- Combination of MAOIs and CNS depressants may enhance sedation and hypotension



Other Warnings/ Precautions

- Use requires low tyramine diet (see Table 2 after Pearls)
- Patient and prescriber must be vigilant to potential interactions with any drug, including antihypertensives and over-the-counter cough/cold preparations
- Over-the-counter medications to avoid include cough and cold preparations, including those containing dextromethorphan, nasal decongestants (tablets, drops, or spray), hay-fever medications, sinus medications, asthma inhalant medications, anti-appetite medications, weight reducing preparations, “pep” pills (see Table 3 after Pearls)
- Hypoglycemia may occur in diabetic patients receiving insulin or oral antidiabetic agents
- Use cautiously in patients receiving reserpine, anesthetics, disulfiram, metrizamide, anticholinergic agents
- Phenelzine is not recommended for use in patients who cannot be monitored closely
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately

- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is taking meperidine (pethidine)
- If patient is taking a sympathomimetic agent or taking guanethidine
- If patient is taking another MAOI
- If patient is taking any agent that can inhibit serotonin reuptake (e.g., SSRIs, sibutramine, tramadol, milnacipran, duloxetine, venlafaxine, clomipramine, etc.)
- If patient is taking diuretics, dextromethorphan
- If patient has pheochromocytoma
- If patient has cardiovascular or cerebrovascular disease
- If patient has frequent or severe headaches
- If patient is undergoing elective surgery and requires general anesthesia
- If patient has a history of liver disease or abnormal liver function tests
- If patient is taking a prohibited drug
- If patient is not compliant with a low-tyramine diet
- If there is a proven allergy to phenelzine

SPECIAL CONSIDERATIONS

Renal Impairment

- Use with caution – drug may accumulate in plasma
- May require lower than usual adult dose

Hepatic Impairment

- Phenelzine should not be used

Cardiac Impairment

- Contraindicated in patients with congestive heart failure or hypertension
- Any other cardiac impairment may require lower than usual adult dose
- Patients with angina pectoris or coronary artery disease should limit their exertion

Elderly

- Initial dose 7.5 mg/day; increase every few days by 7.5–15 mg/day
- Elderly patients may have greater sensitivity to adverse effects
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Not recommended for use under age 16
- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester
- Possible increased incidence of fetal malformations if phenelzine is taken during the first trimester
- Should evaluate patient for treatment with an antidepressant with a better risk/benefit ratio

Breast Feeding

- Some drug is found in mother's breast milk
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Should evaluate patient for treatment with an antidepressant with a better risk/benefit ratio

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Atypical depression
- Severe depression
- Treatment-resistant depression or anxiety disorders

Potential Disadvantages

- Requires compliance to dietary restrictions, concomitant drug restrictions
- Patients with cardiac problems or hypertension
- Multiple daily doses

Primary Target Symptoms

- Depressed mood
- Somatic symptoms
- Sleep and eating disturbances
- Psychomotor retardation
- Morbid preoccupation



Pearls

- MAOIs are generally reserved for second-line use after SSRIs, SNRIs, and combinations of newer antidepressants have failed
- Patient should be advised not to take any prescription or over-the-counter drugs without consulting their doctor because of possible drug interactions with the MAOI
- Headache is often the first symptom of hypertensive crisis
- The rigid dietary restrictions may reduce compliance (see Table 2 after Pearls)
- Mood disorders can be associated with eating disorders (especially in adolescent females), and phenelzine can be used to treat both depression and bulimia
- MAOIs are a viable second-line treatment option in depression, but are not frequently used

- ✿ Myths about the danger of dietary tyramine can be exaggerated, but prohibitions against concomitant drugs often not followed closely enough
- Orthostatic hypotension, insomnia, and sexual dysfunction are often the most troublesome common side effects
- ✿ MAOIs should be for the expert, especially if combining with agents of potential risk (e.g., stimulants, trazodone, TCAs)
- ✿ MAOIs should not be neglected as therapeutic agents for the treatment-resistant
- Although generally prohibited, a heroic but potentially dangerous treatment for severely treatment-resistant patients is for an expert to give a tricyclic/tetracyclic antidepressant other than clomipramine simultaneously with an MAOI for patients who fail to respond to numerous other antidepressants
- Use of MAOIs with clomipramine is always prohibited because of the risk of serotonin syndrome and death
- Amoxapine may be the preferred tricyclic/tetracyclic antidepressant to combine with an MAOI in heroic cases due to its theoretically protective 5HT2A antagonist properties
- If this option is elected, start the MAOI with the tricyclic/tetracyclic antidepressant simultaneously at low doses after appropriate drug washout, then alternately increase doses of these agents every few days to a week as tolerated
- Although very strict dietary and concomitant drug restrictions must be observed to prevent hypertensive crises and serotonin syndrome, the most common side effects of MAOI and tricyclic/tetracyclic combinations may be weight gain and orthostatic hypotension

Table 1. Drugs contraindicated due to risk of serotonin syndrome/toxicity

Do Not Use:			
Antidepressants	Drugs of Abuse	Opioids	Other
SSRIs	MDMA (ecstasy)	Meperidine	Non-subcutaneous sumatriptan
SNRIs	Cocaine	Tramadol	Chlorpheniramine
Clomipramine	Methamphetamine	Methadone	Brompheniramine
St. John's wort	High-dose or injected amphetamine	Fentanyl	Dextromethorphan
			Procarbazine?

PHENELZINE (continued)

Table 2. Dietary guidelines for patients taking MAOIs

Foods to avoid*	Foods allowed
Dried, aged, smoked, fermented, spoiled, or improperly stored meat, poultry, and fish	Fresh or processed meat, poultry, and fish; properly stored pickled or smoked fish
Broad bean pods	All other vegetables
Aged cheeses	Processed cheese slices, cottage cheese, ricotta cheese, yogurt, cream cheese
Tap and unpasteurized beer	Canned or bottled beer and alcohol
Marmite	Brewer's and baker's yeast
Sauerkraut, kimchee	
Soy products/tofu	Peanuts
Banana peel	Bananas, avocados, raspberries
Tyramine-containing nutritional supplement	

*Not necessary for 6-mg transdermal or low-dose oral selegiline

Table 3. Drugs that boost norepinephrine: should only be used with caution with MAOIs

Use With Caution:			
Decongestants	Stimulants	Antidepressants with norepinephrine reuptake inhibition	Other
Phenylephrine	Amphetamines	Most tricyclics	Phentermine
Pseudoephedrine	Methylphenidate	NRIs	Local anesthetics containing vasoconstrictors
	Cocaine	NDRIs	
	Methamphetamine		
	Modafinil		Tapentadol
	Armodafinil		



Suggested Reading

Kennedy SH. Continuation and maintenance treatments in major depression: the neglected role of monoamine oxidase inhibitors. *J Psychiatry Neurosci* 1997;22:127-31.

Lippman SB, Nash K. Monoamine oxidase inhibitor update. Potential adverse food and drug interactions. *Drug Saf* 1990;5:195-204.

Parsons B, Quitkin FM, McGrath PJ, et al. Phenelzine, imipramine, and placebo in borderline patients meeting criteria for atypical depression. *Psychopharmacol Bull* 1989;25:524-34.

THERAPEUTICS

Brands

- Triptil

- Vivactil

see index for additional brand names

Generic? Yes**Class**

- Neuroscience-based Nomenclature: serotonin, norepinephrine reuptake inhibitor
- Tricyclic antidepressant (TCA)
- Predominantly a norepinephrine/noradrenaline reuptake inhibitor

Commonly Prescribed for

(bold for FDA approved)

- **Mental depression**
- Treatment-resistant depression

**How the Drug Works**

- Boosts neurotransmitter norepinephrine/noradrenaline
- Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing noradrenergic neurotransmission
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, protriptyline can increase dopamine neurotransmission in this part of the brain
- A more potent inhibitor of norepinephrine reuptake pump than serotonin reuptake pump (serotonin transporter)
- At high doses may also boost neurotransmitter serotonin and presumably increase serotonergic neurotransmission

How Long Until It Works

- Some evidence it may have an early onset of action with improvement in activity and energy as early as 1 week
- Onset of therapeutic actions usually not immediate, but often delayed 2 to 4 weeks
- If it is not working within 6 to 8 weeks for depression, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Continue treatment until all symptoms are gone (remission)
- Once symptoms gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders may also need to be indefinite

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer

**Best Augmenting Combos for Partial Response or Treatment Resistance**

- Lithium, buspirone, thyroid hormone

Tests

- Baseline ECG is recommended for patients over age 50
- Since tricyclic and tetracyclic antidepressants are frequently associated with weight gain, before starting treatment, weigh all patients and determine if the patient is already overweight (BMI 25.0–29.9) or obese (BMI ≥30)
- Before giving a drug that can cause weight gain to an overweight or obese

PROTRIPTYLINE (continued)

patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–125 mg/dL), diabetes (fasting plasma glucose >126 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management

- ✿ Monitor weight and BMI during treatment
- ✿ While giving a drug to a patient who has gained >5% of initial weight, consider evaluating for the presence of pre-diabetes, diabetes, or dyslipidemia, or consider switching to a different antidepressant
 - EKGs may be useful for selected patients (e.g., those with personal or family history of QTc prolongation; cardiac arrhythmia; recent myocardial infarction; uncompensated heart failure; or taking agents that prolong QTc interval such as pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin, etc.)
 - Patients at risk for electrolyte disturbances (e.g., patients on diuretic therapy) should have baseline and periodic serum potassium and magnesium measurements

SIDE EFFECTS

How Drug Causes Side Effects

- ✿ Anticholinergic activity for protriptyline may be more potent than for some other TCAs and may explain sedative effects, dry mouth, constipation, blurred vision, tachycardia, and hypotension
- Sedative effects and weight gain may be due to antihistamine properties
- Blockade of alpha 1 adrenergic receptors may explain dizziness, sedation, and hypotension
- Cardiac arrhythmias, especially in overdose, may be caused by blockade of ion channels

Notable Side Effects

- Blurred vision, constipation, urinary retention, increased appetite, dry mouth, nausea, diarrhea, heartburn, unusual taste in mouth, weight gain

- Fatigue, weakness, dizziness, sedation, headache, anxiety, nervousness, restlessness
- Sexual dysfunction (impotence, change in libido)
- Sweating, rash, itching



Life-Threatening or Dangerous Side Effects

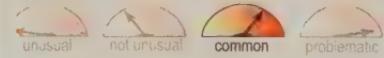
- Paralytic ileus, hyperthermia (TCAs + anticholinergic agents)
- Lowered seizure threshold and rare seizures
- Orthostatic hypotension, sudden death, arrhythmias, tachycardia
- QTc prolongation
- Hepatic failure, extrapyramidal symptoms
- Increased intraocular pressure
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Many experience and/or can be significant in amount
- Can increase appetite and carbohydrate craving

Sedation



- Many experience and/or can be significant in amount
- ✿ Not as sedating as other TCAs; more likely to be activating than other TCAs

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- Switch to an SSRI or newer antidepressant

Best Augmenting Agents for Side Effects

- Trazodone or a hypnotic for insomnia
- Benzodiazepines for agitation and anxiety
- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 15–40 mg/day in 3–4 divided doses

Dosage Forms

- Tablets 5 mg, 10 mg

How to Dose

- Initial 15 mg/day in divided doses; increase morning dose as needed; maximum dose 60 mg/day



Dosing Tips

✳ Be aware that among this class of agents (tricyclic/tetracyclic antidepressants), protriptyline has uniquely low dosing (15–40 mg/day for protriptyline compared to 75–300 mg/day for most other tricyclic/tetracyclic antidepressants)

✳ Be aware that among this class of agents (tricyclic/tetracyclic antidepressants), protriptyline has uniquely frequent dosing (3–4 times a day compared to once daily for most other tricyclic/tetracyclic antidepressants)

- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar disorder, and switch to a mood stabilizer or an atypical antipsychotic

Overdose

- Death may occur; CNS depression, convulsions, cardiac dysrhythmias, severe hypotension, EKG changes, coma

Long-Term Use

- Safe

Habit Forming

- No

How to Stop

- Taper to avoid withdrawal effects
- Even with gradual dose reduction some withdrawal symptoms may appear within the first 2 weeks
- Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation
- If withdrawal symptoms emerge during discontinuation, raise dose to stop

symptoms and then restart withdrawal much more slowly

Pharmacokinetics

- Substrate for CYP450 2D6
- Half-life approximately 74 hours



Drug Interactions

- Tramadol increases the risk of seizures in patients taking TCAs
- Use of TCAs with anticholinergic drugs may result in paralytic ileus or hyperthermia
- Fluoxetine, paroxetine, bupropion, duloxetine, and other 2D6 inhibitors may increase TCA concentrations
- Cimetidine may increase plasma concentrations of TCAs and cause anticholinergic symptoms
- Phenothiazines or haloperidol may raise TCA blood concentrations
- May alter effects of antihypertensive drugs; may inhibit hypotensive effects of clonidine
- Use with sympathomimetic agents may increase sympathetic activity
- Methylphenidate may inhibit metabolism of TCAs
- Activation and agitation, especially following switching or adding antidepressants, may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of protriptyline



Other Warnings/ Precautions

- Add or initiate other antidepressants with caution for up to 2 weeks after discontinuing protriptyline
- Generally, do not use with MAOIs, including 14 days after MAOIs are stopped; do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing protriptyline
- Use with caution in patients with history of seizures, urinary retention, angle-closure glaucoma, hyperthyroidism
- TCAs can increase QTc interval, especially at toxic doses, which can be attained not

only by overdose but also by combining with drugs that inhibit TCA metabolism via CYP450 2D6, potentially causing torsade de pointes-type arrhythmia or sudden death

- Because TCAs can prolong QTc interval, use with caution in patients who have bradycardia or who are taking drugs that can induce bradycardia (e.g., beta blockers, calcium channel blockers, clonidine, digitalis)
- Because TCAs can prolong QTc interval, use with caution in patients who have hypokalemia and/or hypomagnesemia or who are taking drugs that can induce hypokalemia and/or magnesemia (e.g., diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactide)
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is recovering from myocardial infarction
- If patient is taking agents capable of significantly prolonging QTc interval (e.g., pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin)
- If there is a history of QTc prolongation or cardiac arrhythmia, recent acute myocardial infarction, uncompensated heart failure
- If patient is taking drugs that inhibit TCA metabolism, including CYP450 2D6 inhibitors, except by an expert
- If there is reduced CYP450 2D6 function, such as patients who are poor 2D6 metabolizers, except by an expert and at low doses
- If there is a proven allergy to protriptyline

SPECIAL POPULATIONS

Renal Impairment

- Use with caution; may need to lower dose
- Patient may need to be monitored closely

Hepatic Impairment

- Use with caution; may need to lower dose
- Patient may need to be monitored closely

Cardiac Impairment

- Baseline ECG is recommended
 - TCAs have been reported to cause arrhythmias, prolongation of conduction time, orthostatic hypotension, sinus tachycardia, and heart failure, especially in the diseased heart
 - Myocardial infarction and stroke have been reported with TCAs
 - TCAs produce QTc prolongation, which may be enhanced by the existence of bradycardia, hypokalemia, congenital or acquired long QTc interval, which should be evaluated prior to administering protriptyline
 - Use with caution if treating concomitantly with a medication likely to produce prolonged bradycardia, hypokalemia, slowing of intracardiac conduction, or prolongation of the QTc interval
 - Avoid TCAs in patients with a known history of QTc prolongation, recent acute myocardial infarction, and uncompensated heart failure
 - TCAs may cause a sustained increase in heart rate in patients with ischemic heart disease and may worsen (decrease) heart rate variability, an independent risk of mortality in cardiac populations
 - Since SSRIs may improve (increase) heart rate variability in patients following a myocardial infarct and may improve survival as well as mood in patients with acute angina or following a myocardial infarction, these are more appropriate agents for cardiac population than tricyclic/tetracyclic antidepressants
- * Risk/benefit ratio may not justify use of TCAs in cardiac impairment

Elderly

- Baseline ECG is recommended for patients over age 50
- May be more sensitive to anticholinergic, cardiovascular, hypotensive, and sedative effects

- Recommended dose is between 15–20 mg/day; doses >20 mg/day require close monitoring of patient
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Not recommended for use under age 12
- Not intended for use under age 6
- Several studies show lack of efficacy of TCAs for depression
- Some cases of sudden death have occurred in children taking TCAs
- Recommended dose: 15–20 mg/day



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Crosses the placenta
- Adverse effects have been reported in infants whose mothers took a TCA (lethargy, withdrawal symptoms, fetal malformations)
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence

of depression, maternal health, infant bonding) to the mother and child

- For many patients this may mean continuing treatment during pregnancy

Breast Feeding

- Some drug is found in mother's breast milk
- * Recommended either to discontinue drug or bottle feed
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Severe or treatment-resistant depression
- Withdrawn, anergic patients

Potential Disadvantages

- Pediatric, geriatric, and cardiac patients
- Patients concerned with weight gain
- Patients noncompliant with 3–4 times daily dosing

Primary Target Symptoms

- Depressed mood



Pearls

- TCAs are no longer generally considered a first-line treatment option for depression because of their side effect profile
- TCAs continue to be useful for severe or treatment-resistant depression
- * Has some potential advantages for withdrawn, anergic patients
- * May have a more rapid onset of action than some other TCAs
- * May aggravate agitation and anxiety more than some other TCAs

- ✿ May have more anticholinergic side effects, hypotension, and tachycardia than some other TCAs
- Noradrenergic reuptake inhibitors such as protriptyline can be used as a second-line treatment for smoking cessation, cocaine dependence, and attention deficit disorder
- TCAs may aggravate psychotic symptoms
- Alcohol should be avoided because of additive CNS effects
- Underweight patients may be more susceptible to adverse cardiovascular effects
- Children, patients with inadequate hydration, and patients with cardiac disease may be more susceptible to TCA-induced cardiotoxicity than healthy adults
- For the expert only: a heroic treatment (but potentially dangerous) for severely treatment-resistant patients is to give simultaneously with MAOIs for patients who fail to respond to numerous other antidepressants, but generally recommend a different TCA than protriptyline for this use
- If this option is elected, start the MAOI with the tricyclic/tetracyclic antidepressant simultaneously at low doses after appropriate drug washout, then alternately increase doses of these agents every few days to a week as tolerated
- Although very strict dietary and concomitant drug restrictions must be observed to prevent hypertensive crises and serotonin syndrome, the most common side effects of MAOI and tricyclic/tetracyclic antidepressant combinations may be weight gain and orthostatic hypotension
- Patients on TCAs should be aware that they may experience symptoms such as photosensitivity or blue-green urine
- SSRIs may be more effective than TCAs in women, and TCAs may be more effective than SSRIs in men
- Since tricyclic/tetracyclic antidepressants are substrates for CYP450 2D6, and 7% of the population (especially Caucasians) may have a genetic variant leading to reduced activity of 2D6, such patients may not safely tolerate normal doses of tricyclic/tetracyclic antidepressants and may require dose reduction
- Phenotypic testing may be necessary to detect this genetic variant prior to dosing with a tricyclic/tetracyclic antidepressant, especially in vulnerable populations such as children, elderly, cardiac populations, and those on concomitant medications
- Patients who seem to have extraordinarily severe side effects at normal or low doses may have this phenotypic CYP450 2D6 variant and require low doses or switching to another antidepressant not metabolized by 2D6



Suggested Reading

Anderson IM. Meta-analytical studies on new antidepressants. *Br Med Bull* 2001;57:161–78.

Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *J Aff Disorders* 2000;58:19–36.

Rudorfer MV, Potter WZ. Metabolism of tricyclic antidepressants. *Cell Mol Neurobiol* 1999;19(3):373–409.

THERAPEUTICS

- Brands**
- Seroquel
 - Seroquel XR

see index for additional brand names

Generic? Yes



Class

- Neuroscience-based Nomenclature: dopamine, serotonin multimodal (DS-MM)
- Atypical antipsychotic (serotonin-dopamine antagonist; second-generation antipsychotic; also a mood stabilizer)

Commonly Prescribed for

(bold for FDA approved)

- **Acute schizophrenia in adults (quetiapine, quetiapine XR) and ages 13–17 (quetiapine)**
- **Schizophrenia maintenance (quetiapine XR)**
- **Acute mania in adults (quetiapine and quetiapine XR, monotherapy and adjunct to lithium or valproate) and ages 10–17 (quetiapine, monotherapy and adjunct to lithium or valproate)**
- **Bipolar maintenance (quetiapine, quetiapine XR)**
- **Bipolar depression (quetiapine, quetiapine XR)**
- **Depression (quetiapine XR, adjunct)**
- Other psychotic disorders
- Mixed mania
- Behavioral disturbances in dementias
- Behavioral disturbances in Parkinson's disease and Lewy body dementia
- Psychosis associated with levodopa treatment in Parkinson's disease
- Behavioral disturbances in children and adolescents
- Disorders associated with problems with impulse control
- Severe treatment-resistant anxiety



How the Drug Works

- Blocks dopamine 2 receptors, reducing positive symptoms of psychosis and stabilizing affective symptoms
- Blocks serotonin 2A receptors, causing enhancement of dopamine release in certain brain regions and thus reducing motor side effects and possibly improving cognitive and affective symptoms

★ Interactions at a myriad of other neurotransmitter receptors may contribute to quetiapine's efficacy in treatment-resistant depression or bipolar depression, especially 5HT1A partial agonist action, norepinephrine reuptake blockade and 5HT2C antagonist and 5HT7 antagonist properties

★ Specifically, actions at 5HT1A receptors may contribute to efficacy for cognitive and affective symptoms in some patients, especially at moderate to high doses

How Long Until It Works

- Psychotic and manic symptoms can improve within 1 week, but it may take several weeks for full effect on behavior as well as on cognition and affective stabilization
- Classically recommended to wait at least 4–6 weeks to determine efficacy of drug, but in practice some patients require up to 16–20 weeks to show a good response, especially on cognitive symptoms

If It Works

- Most often reduces positive symptoms in schizophrenia but does not eliminate them
- Can improve negative symptoms, as well as aggressive, cognitive, and affective symptoms in schizophrenia
- Most schizophrenic patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third
- Perhaps 5–15% of schizophrenic patients can experience an overall improvement of greater than 50–60%, especially when receiving stable treatment for more than a year
- Such patients are considered super-responders or "awakeners" since they may be well enough to be employed, live independently, and sustain long-term relationships
- Many bipolar patients may experience a reduction of symptoms by half or more
- Continue treatment until reaching a plateau of improvement
- After reaching a satisfactory plateau, continue treatment for at least a year after first episode of psychosis
- For second and subsequent episodes of psychosis, treatment may need to be indefinite

- Even for first episodes of psychosis, it may be preferable to continue treatment indefinitely to avoid subsequent episodes
- Treatment may not only reduce mania but also prevent recurrences of mania in bipolar disorder

If It Doesn't Work

- Try one of the other atypical antipsychotics (risperidone, olanzapine, ziprasidone, aripiprazole, paliperidone, amisulpride, asenapine, iloperidone, lurasidone)
- If 2 or more antipsychotic monotherapies do not work, consider clozapine
- Some patients may require treatment with a conventional antipsychotic
- If no first-line atypical antipsychotic is effective, consider higher doses or augmentation with valproate or lamotrigine
- Consider noncompliance and switch to another antipsychotic with fewer side effects or to an antipsychotic that can be given by depot injection
- Consider initiating rehabilitation and psychotherapy such as cognitive remediation
- Consider presence of concomitant drug abuse



Best Augmenting Combos for Partial Response or Treatment Resistance

- Valproic acid (valproate, divalproex, divalproex ER)
- Other mood-stabilizing anticonvulsants (carbamazepine, oxcarbazepine, lamotrigine)
- Lithium
- Benzodiazepines

Tests

Before starting an atypical antipsychotic

- Weigh all patients and track BMI during treatment
- Get baseline personal and family history of diabetes, obesity, dyslipidemia, hypertension, and cardiovascular disease
- Get waist circumference (at umbilicus), blood pressure, fasting plasma glucose, and fasting lipid profile
- Determine if the patient is
 - overweight (BMI 25.0–29.9)
 - obese (BMI ≥ 30)
 - has pre-diabetes (fasting plasma glucose 100–125 mg/dL)

- has diabetes (fasting plasma glucose >126 mg/dL)
- has hypertension (BP $>140/90$ mm Hg)
- has dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol)
- Treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management

Monitoring after starting an atypical antipsychotic

- BMI monthly for 3 months, then quarterly
- Consider monitoring fasting triglycerides monthly for several months in patients at high risk for metabolic complications and when initiating or switching antipsychotics
- Blood pressure, fasting plasma glucose, fasting lipids within 3 months and then annually, but earlier and more frequently for patients with diabetes or who have gained $>5\%$ of initial weight
- Treat or refer for treatment and consider switching to another atypical antipsychotic for patients who become overweight, obese, pre-diabetic, diabetic, hypertensive, or dyslipidemic while receiving an atypical antipsychotic
- Even in patients without known diabetes, be vigilant for the rare but life-threatening onset of diabetic ketoacidosis, which always requires immediate treatment, by monitoring for the rapid onset of polyuria, polydipsia, weight loss, nausea, vomiting, dehydration, rapid respiration, weakness, and clouding of sensorium, even coma
- Although US manufacturer recommends 6-month eye checks for cataracts, clinical experience suggests this may be unnecessary
- Patients with low white blood cell count (WBC) or history of drug-induced leucopenia/neutropenia should have complete blood count (CBC) monitored frequently during the first few months and quetiapine should be discontinued at the first sign of decline of WBC in the absence of other causative factors

SIDE EFFECTS**How Drug Causes Side Effects**

- By blocking histamine 1 receptors in the brain, it can cause sedation and possibly weight gain
- By blocking alpha 1 adrenergic receptors, it can cause dizziness, sedation, and hypotension
- By blocking muscarinic 1 receptors, it can cause dry mouth, constipation, and sedation
- By blocking dopamine 2 receptors in the striatum, it can cause motor side effects (rare)
- Mechanism of weight gain and increased incidence of diabetes and dyslipidemia with atypical antipsychotics is unknown

Notable Side Effects

- Dose-dependent weight gain
- May increase risk for diabetes and dyslipidemia
- Dizziness, sedation
- Dry mouth, constipation
- Dyspepsia, abdominal pain
- Tachycardia
- Orthostatic hypotension, usually during initial dose titration
- Theoretical risk of tardive dyskinesia

**Life-Threatening or Dangerous Side Effects**

- Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking atypical antipsychotics
- Rare neuroleptic malignant syndrome (much reduced risk compared to conventional antipsychotics)
- Rare seizures
- Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis

Weight Gain

- Many patients experience and/or can be significant in amount at effective antipsychotic doses
- Can become a health problem in some
- May be less than for some antipsychotics, more than for others

Sedation

- Frequent and can be significant in amount
- Some patients may not tolerate it
- More than for some other antipsychotics, but never say always as not a problem in everyone
- Can wear off over time
- Can reemerge as dose increases and then wear off again over time
- Not necessarily increased as dose is raised

What to Do About Side Effects

- Wait
- Wait
- Wait
- Usually dosed twice daily, so take more of the total daily dose at bedtime to help reduce daytime sedation
- Start dosing low and increase slowly as side effects wear off at each dosing increment
- Weight loss, exercise programs, and medical management for high BMIs, diabetes, dyslipidemia
- Switch to another atypical antipsychotic

Best Augmenting Agents for Side Effects

- Many side effects cannot be improved with an augmenting agent

DOSING AND USE**Usual Dosage Range**

- 400–800 mg/day in 1 (quetiapine XR) or 2 (quetiapine) doses for schizophrenia
- 400–800 mg/day in 1 (quetiapine XR) or 2 (quetiapine) doses for bipolar mania
- 300 mg once daily for bipolar depression

Dosage Forms

- Tablets 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg
- Extended-release tablets 50 mg, 150 mg, 200 mg, 300 mg, 400 mg

How to Dose

- (According to manufacturer for quetiapine in schizophrenia): initial 25 mg/day twice a day; increase by 25–50 mg twice a day

each day until desired efficacy is reached; maximum approved dose 800 mg/day

- In practice, can start adults with schizophrenia under age 65 with same doses as recommended for acute bipolar mania
- (According to manufacturer for quetiapine in acute bipolar mania): initiate in twice daily doses, totaling 100 mg/day on day 1, increasing to 400 mg/day on day 4 in increments of up to 100 mg/day; further dosage adjustments up to 800 mg/day by day 6 should be in increments of no greater than 200 mg/day
- Bipolar depression for quetiapine and quetiapine XR: once daily at bedtime; titrate as needed to reach 300 mg/day by day 4
- Quetiapine XR in schizophrenia and acute mania: initial 300 mg once daily, preferably in the evening; can increase by 300 mg/day each day until desired efficacy is reached; maximum approved dose 800 mg/day
- See also The Art of Switching section, after Pearls



Dosing Tips

- More may be much more: clinical practice suggests quetiapine often underdosed, then switched prior to adequate trials
- Clinical practice suggests that at low doses it may be a sedative hypnotic, possibly due to potent H1 antihistamine actions, but this can risk numerous antipsychotic-related side effects and there are many other options
- Initial target dose of 400–800 mg/day should be reached in most cases to optimize the chances of success in treating acute psychosis and acute mania, but many patients are not adequately dosed in clinical practice
- Many patients do well with immediate-release as a single daily oral dose, usually at bedtime
- Recommended titration to 400 mg/day by the fourth day can often be achieved when necessary to control acute symptoms
- Rapid dose escalation in manic or psychotic patients may lessen sedative side effects
- Higher doses generally achieve greater response for manic or psychotic symptoms
- In contrast, some patients with bipolar depression may respond well to doses

less than 300 mg/day and as little as 25 mg/day

- Dosing in major depression may be even lower than in bipolar depression, and dosing may be even lower still in GAD
- Occasional patients may require more than 800–1,200 mg/day for psychosis or mania
- Rather than raise the dose above these levels in acutely agitated patients requiring acute antipsychotic actions, consider augmentation with a benzodiazepine or conventional antipsychotic, either orally or intramuscularly
- Rather than raise the dose above these levels in partial responders, consider augmentation with a mood-stabilizing anticonvulsant such as valproate or lamotrigine
- Children and elderly should generally be dosed at the lower end of the dosage spectrum
- Quetiapine XR is controlled-release and therefore should not be chewed or crushed but rather should be swallowed whole
- Quetiapine XL may theoretically generate increased concentrations of active metabolite norquetiapine, with theoretically improved profile for affective and anxiety disorders
- Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³

Overdose

- Rarely lethal in monotherapy overdose; sedation, slurred speech, hypotension

Long-Term Use

- Approved for long-term maintenance in schizophrenia and bipolar disorder, and often used for long-term maintenance in various behavioral disorders

Habit Forming

- No

How to Stop

- See also the Switching section of individual agents for how to stop quetiapine
- Rapid discontinuation may lead to rebound psychosis and worsening of symptoms

Pharmacokinetics

- Parent drug has 6–7 hour half-life
- Substrate for CYP450 3A4
- Food may slightly increase absorption



Drug Interactions

- CYP450 3A inhibitors and CYP450 2D6 inhibitors may reduce clearance of quetiapine and thus raise quetiapine plasma levels, but dosage reduction of quetiapine usually not necessary
- May increase effect of anti-hypertensive agents
- There are case reports of increased international normalized ratio (INR) (used to monitor the degree of anticoagulation) when quetiapine is coadministered with warfarin, which is also a substrate of CYP450 3A4



Other Warnings/ Precautions

- In the USA, manufacturer recommends examination for cataracts before and every 6 months after initiating quetiapine, but this does not seem to be necessary in clinical practice
- Quetiapine should be used cautiously in patients at risk for aspiration pneumonia, as dysphagia has been reported
- Priapism has been reported
- Use with caution in patients with known cardiovascular disease, cerebrovascular disease
- Use with caution in patients with conditions that predispose to hypotension (dehydration, overheating)
- Monitor patients for activation of suicidal ideation, especially children and adolescents
- Avoid use with drugs that increase the QT interval and in patients with risk factors for prolonged QT interval

Do Not Use

- If there is a proven allergy to quetiapine

SPECIAL CONSIDERATIONS

Renal Impairment

- No dose adjustment required

Hepatic Impairment

- Downward dose adjustment may be necessary

Cardiac Impairment

- Drug should be used with caution because of risk of orthostatic hypotension

Elderly

- Lower dose is generally used (e.g., 25–100 mg twice a day), although higher doses may be used if tolerated
- Although atypical antipsychotics are commonly used for behavioral disturbances in dementia, no agent has been approved for treatment of elderly patients with dementia-related psychosis
- Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo, and also have an increased risk of cerebrovascular events



Children and Adolescents

- Approved for use in schizophrenia (ages 13 and older) and manic/mixed episodes (ages 10 and older)
- Clinical experience and early data suggest quetiapine may be safe and effective for behavioral disturbances in children and adolescents
- Children and adolescents using quetiapine may need to be monitored more often than adults
- Use with caution, observing for activation of suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- May tolerate lower doses better



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- There is a risk of abnormal muscle movements and withdrawal symptoms

QUETIAPINE (continued)

in newborns whose mothers took an antipsychotic during the third trimester; symptoms may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty feeding

- Psychotic symptoms may worsen during pregnancy and some form of treatment may be necessary
- Quetiapine may be preferable to anticonvulsant mood stabilizers if treatment is required during pregnancy
- National Pregnancy Registry for Atypical Antipsychotics: 1-866-961-2388 or <http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/>

Breast Feeding

- Unknown if quetiapine is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- Recommended either to discontinue drug or bottle feed
- Infants of women who choose to breast feed while on quetiapine should be monitored for possible adverse effects

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Bipolar depression
- Some cases of psychosis and bipolar disorder refractory to treatment with other antipsychotics
- Patients with Parkinson's disease who need an antipsychotic or mood stabilizer
- Patients with Lewy body dementia who need an antipsychotic or mood stabilizer

Potential Disadvantages

- Patients requiring rapid onset of action
- Patients who have difficulty tolerating sedation

Primary Target Symptoms

- Positive symptoms of psychosis
- Negative symptoms of psychosis
- Cognitive symptoms
- Unstable mood (both depression and mania)
- Aggressive symptoms
- Insomnia and anxiety



Pearls

- May be the preferred antipsychotic for psychosis in Parkinson's disease and Lewy body dementia
- Anecdotal reports of efficacy in treatment-refractory cases and positive symptoms of psychoses other than schizophrenia
- Efficacy may be underestimated for psychosis and mania since quetiapine is often under-dosed in clinical practice
- Approved in bipolar depression
- The active metabolite of quetiapine, norquetiapine, has the additional properties of norepinephrine reuptake inhibition and antagonism of 5HT2C receptors, which may contribute to therapeutic effects for mood and cognition
- Dosing differs depending on the indication, with high-dose mechanisms including robust blockade of D2 receptors above 60% occupancy and equal or greater 5HT2A blockade; medium-dose mechanisms including moderate amounts of NET inhibition combined with 5HT2C antagonism and 5HT1A partial agonism; and low-dose mechanisms including H1 antagonism and 5HT1A partial agonism and, to a lesser extent, NET inhibition and 5HT2C antagonism
- More sedation than some other antipsychotics, which may be of benefit in acutely manic or psychotic patients but not for stabilized patients in long-term maintenance
- Essentially no motor side effects or prolactin elevation
- May have less weight gain than some antipsychotics, more than others
- Controversial as to whether quetiapine has more or less risk of diabetes and dyslipidemia than some other antipsychotics
- Commonly used at low doses to augment other atypical antipsychotics, but such antipsychotic polypharmacy has not been systematically studied and can be quite expensive
- Anecdotal reports of efficacy in PTSD, including symptoms of sleep disturbance and anxiety
- Patients with inadequate responses to atypical antipsychotics may benefit from determination of plasma drug levels and,

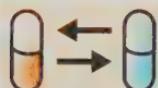
if low, a dosage increase even beyond the usual prescribing limits

- For treatment-resistant patients, especially those with impulsivity, aggression, violence, and self-harm, long-term polypharmacy with 2 atypical antipsychotics or with 1

atypical antipsychotic and 1 conventional antipsychotic may be useful or even necessary while closely monitoring

- In such cases, it may be beneficial to combine 1 depot antipsychotic with 1 oral antipsychotic

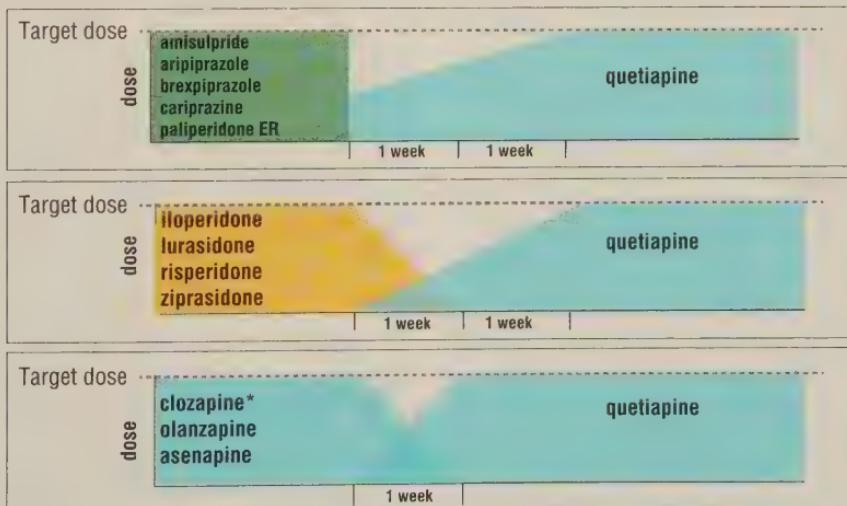
THE ART OF SWITCHING



Switching from Oral Antipsychotics to Quetiapine

- With aripiprazole, amisulpride, and paliperidone ER, immediate stop is possible; begin quetiapine at middle dose
- With risperidone, ziprasidone, iloperidone, and lurasidone, it is generally advisable to begin quetiapine gradually, titrating over at least 2 weeks to allow patients to become tolerant to the sedating effect
- For more convenient dosing, patients who are currently being treated with divided doses of immediate-release tablets may be switched to extended-release quetiapine at the equivalent total daily dose taken once daily

*May need to taper clozapine slowly over 4 weeks or longer





Suggested Reading

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THERAPEUTICS

- Brands**
 - Norebox
 - Edronax

see index for additional brand names

Generic? No



Class

- Neuroscience-based Nomenclature: norepinephrine reuptake inhibitor (N-RI)
- Selective norepinephrine reuptake inhibitor (NRI); antidepressant

Commonly Prescribed for

(bold for FDA approved)

- Major depressive disorder
- Dysthymia
- Panic disorder
- Attention deficit hyperactivity disorder (ADHD)



How the Drug Works

- Boosts neurotransmitter norepinephrine/noradrenaline and may also increase dopamine in prefrontal cortex
- Blocks norepinephrine reuptake pump (norepinephrine transporter)
- Presumably, this increases noradrenergic neurotransmission
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex which largely lacks dopamine transporters, reboxetine can increase dopamine neurotransmission in this part of the brain

How Long Until It Works

- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Continue treatment until all symptoms are gone (remission)

- Once symptoms gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer



Best Augmenting Combos for Partial Response or Treatment Resistance

- Trazodone, especially for insomnia
- SSRIs, SNRIs, mirtazapine (use combinations of antidepressants with caution as this may activate bipolar disorder and suicidal ideation)
- Modafinil, especially for fatigue, sleepiness, and lack of concentration
- Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression or treatment-resistant depression
- Benzodiazepines for anxiety
- Hypnotics for insomnia
- Classically, lithium, buspirone, or thyroid hormone

Tests

- None for healthy individuals

SIDE EFFECTS

How Drug Causes Side Effects

- Norepinephrine increases in parts of the brain and body and at receptors other than those that cause therapeutic actions

(e.g., unwanted actions of norepinephrine on acetylcholine release causing constipation and dry mouth, etc.)

- Most side effects are immediate but often go away with time

Notable Side Effects

- Insomnia, dizziness, anxiety, agitation
- Dry mouth, constipation
- Urinary hesitancy, urinary retention
- Sexual dysfunction (impotence)
- Dose-dependent hypotension



Life-Threatening or Dangerous Side Effects

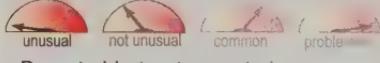
- Rare seizures
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Reported but not expected

Sedation



- Reported but not expected

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- In a few weeks, switch or add other drugs

Best Augmenting Agents for Side Effects

- For urinary hesitancy, give an alpha 1 blocker such as tamsulosin
- Often best to try another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
- Trazodone or a hypnotic for drug-induced insomnia
- Benzodiazepines for drug-induced anxiety and activation
- Mirtazapine for drug-induced insomnia or anxiety

- Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of reboxetine

DOSING AND USE

Usual Dosage Range

- 8 mg/day in 2 doses (10 mg usual maximum daily dose)

Dosage Forms

- Tablet 2 mg, 4 mg scored

How to Dose

- Initial 2 mg/day twice a day for 1 week, 4 mg/day twice a day for second week



Dosing Tips

- When switching from another antidepressant or adding to another antidepressant, dosing may need to be lower and titration slower to prevent activating side effects (e.g., 2 mg in the daytime for 2–3 days, then 2 mg bid for 1–2 weeks)
- Give second daily dose in late afternoon rather than at bedtime to avoid undesired activation or insomnia in the evening
- May not need full dose of 8 mg/day when given in conjunction with another antidepressant
- Some patients may need 10 mg/day or more if well tolerated without orthostatic hypotension and if additional efficacy is seen at high doses in difficult cases
- Early dosing in patients with panic and anxiety may need to be lower and titration slower, perhaps with the use of concomitant short-term benzodiazepines to increase tolerability

Overdose

- Postural hypotension, anxiety, hypertension

Long-Term Use

- Safe

Habit Forming

- No

How to Stop

- Taper not necessary

Pharmacokinetics

- Metabolized by CYP450 3A4
- Inhibits CYP450 2D6 and 3A4 at high doses
- Elimination half-life approximately 13 hours

**Drug Interactions**

- Tramadol increases the risk of seizures in patients taking an antidepressant
- May need to reduce reboxetine dose or avoid concomitant use with inhibitors of CYP450 3A4, such as azole and antifungals, macrolide antibiotics, fluvoxamine, nefazodone, fluoxetine, sertraline, etc.
- Via CYP450 2D6 inhibition, reboxetine could theoretically interfere with the analgesic actions of codeine, and increase the plasma levels of some beta blockers and of atomoxetine and TCAs
- Via CYP450 2D6 inhibition, reboxetine could theoretically increase concentrations of thioridazine and cause dangerous cardiac arrhythmias
- Via CYP450 3A4 inhibition, reboxetine may increase the levels of alprazolam, buspirone, and triazolam
- Via CYP450 3A4 inhibition, reboxetine could theoretically increase concentrations of certain cholesterol lowering HMG CoA reductase inhibitors, especially simvastatin, atorvastatin, and lovastatin, but not pravastatin or fluvastatin, which would increase the risk of rhabdomyolysis; thus, coadministration of reboxetine with certain HMG CoA reductase inhibitors should proceed with caution
- Via CYP450 3A4 inhibition, reboxetine could theoretically increase the concentrations of pimozide, and cause QTc prolongation and dangerous cardiac arrhythmias

- Use with ergotamine may increase blood pressure
- Hypokalemia may occur if reboxetine is used with diuretics
- Use with caution with MAO inhibitors, including 14 days after MAOIs are stopped

**Other Warnings/
Precautions**

- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- Use with caution in patients with urinary retention, benign prostatic hyperplasia, glaucoma, epilepsy
- Use with caution with drugs that lower blood pressure
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient has angle-closure glaucoma
- If patient is taking an MAOI (except as noted under drug interactions)
- If patient is taking pimozide or thioridazine
- If there is a proven allergy to reboxetine

DRUG-DRUG INTERACTIONS**Renal Impairment**

- Plasma concentrations are increased
- May need to lower dose

Hepatic Impairment

- Plasma concentrations are increased
- May need to lower dose

Cardiac Impairment

- Use with caution

Elderly

- Lower dose is recommended (4–6 mg/day)
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older

**Children and Adolescents**

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- No guidelines for children; safety and efficacy have not been established

**Pregnancy**

- No controlled studies in humans
- Not generally recommended for use during pregnancy, especially during first trimester
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy

Breast Feeding

- Some drug is found in mother's breast milk
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients, this may mean continuing treatment during breast feeding

Potential Advantages

- Tired, unmotivated patients
- Patients with cognitive disturbances
- Patients with psychomotor retardation

Potential Disadvantages

- Patients unable to comply with twice daily dosing
- Patients unable to tolerate activation

Primary Target Symptoms

- Depressed mood
- Energy, motivation, and interest
- Suicidal ideation
- Cognitive disturbance
- Psychomotor retardation

**Pearls**

- May be effective if SSRIs have failed or for SSRI "poop-out"
- May be more likely than SSRIs to improve social and work functioning
- Reboxetine is a mixture of an active and an inactive enantiomer, and the active enantiomer may be developed in future clinical testing
- Side effects may appear "anticholinergic," but reboxetine does not directly block muscarinic receptors
- Constipation, dry mouth, and urinary retention are noradrenergic, due in part to peripheral alpha 1 receptor stimulation causing decreased acetylcholine release
- Thus, antidotes for these side effects can be alpha 1 antagonists such as tamsulosin, especially for urinary retention in men over 50 with borderline urine flow
- Novel use of reboxetine may be for attention deficit disorder, analogous to the actions of another norepinephrine selective reuptake inhibitor, atomoxetine, but few controlled studies
- Another novel use may be for neuropathic pain, alone or in combination with other antidepressants, but few controlled studies
- Some studies suggest efficacy in panic disorder



Suggested Reading

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THERAPEUTICS

Brands

- EMSAM

- Eldepryl

see index for additional brand names

Generic? Yes (oral only)**Class**

- Neuroscience-based Nomenclature: dopamine, serotonin, norepinephrine enzyme inhibitor (DSM-EI)
- Transdermal: tissue selective monoamine oxidase (MAO) inhibitor (MAO-A and MAO-B inhibitor in brain and relatively selective MAO-B inhibitor in gut)
- Oral: selective MAO-B inhibitor

Commonly Prescribed for

(bold for FDA approved)

- Major depressive disorder (transdermal)**
- Oral: Parkinson's disease or symptomatic parkinsonism (adjunctive)**
- Treatment-resistant depression
- Panic disorder (transdermal)
- Social anxiety disorder (transdermal)
- Treatment-resistant anxiety disorders (transdermal)
- Alzheimer disease and other dementias (oral)

**How the Drug Works**

- Transdermal selegiline (recommended doses): in the brain, irreversibly inhibits both MAO-A and MAO-B from breaking down norepinephrine, serotonin, and dopamine, which presumably boosts noradrenergic, serotonergic, and dopaminergic neurotransmission
- Transdermal selegiline (recommended doses): in the gut, is a relatively selective irreversible inhibitor of MAO-B (intestine and liver), reducing the chances of dietary interactions with the MAO-A substrate tyramine
- Oral: at recommended doses, selectively and irreversibly blocks MAO-B, which presumably boosts dopaminergic neurotransmission
- Oral: above recommended doses, irreversibly blocks both MAO-A and MAO-B from breaking down norepinephrine, serotonin, and dopamine while

simultaneously blocking metabolism of tyramine in the gut

- Thus, high dose oral administration is not tissue selective and is not MAO-A sparing in the gut, and may interact with tyramine-containing foods to cause hypertension

How Long Until It Works

- Onset of therapeutic actions in depression with transdermal administration is usually not immediate, but often delayed 2–4 weeks or longer
- If it is not working for depression within 6–8 weeks, it may require a dosage increase or it may not work at all
- May continue to work in depression for many years to prevent relapse of symptoms
- Can enhance the actions of levodopa in Parkinson's disease within a few weeks of initiating oral dosing
- Theoretical slowing of functional loss in both Parkinson's disease and Alzheimer disease is a provocative possibility under investigation and would take many months or more than a year to observe

If It Works

- The goal of treatment in depression is complete remission of current symptoms as well as prevention of future relapses
- Treatment of depression most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Continue treatment of depression until all symptoms of depression are gone (remission)
- Once symptoms of depression are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Continue use in Parkinson's disease as long as there is evidence that selegiline is favorably enhancing the actions of levodopa
- Use of selegiline to slow functional loss in Parkinson's disease or Alzheimer disease would be long-term if proven effective for this use

If It Doesn't Work

- Many depressed patients have only a partial response where some symptoms

are improved but others persist (especially insomnia, fatigue, and problems concentrating)

- Other depressed patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some depressed patients who have an initial response may relapse even though they continue treatment, sometimes called “poop out”
- For depression, consider increasing dose, switching to another agent or adding an appropriate augmenting agent, psychotherapy, and evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer
- Use alternate treatments for Parkinson’s disease or Alzheimer disease



Best Augmenting Combos for Partial Response or Treatment Resistance

- Augmentation of selegiline has not been systematically studied in depression, and this is something for the expert, to be done with caution and with careful monitoring
- A stimulant such as d-amphetamine or methylphenidate (with caution and by experts only as use of stimulants with selegiline is listed as a warning; may activate bipolar disorder and suicidal ideation; may elevate blood pressure)
- Lithium
- Mood-stabilizing anticonvulsants
- Atypical antipsychotics (with special caution for those agents with monoamine reuptake blocking properties, such as ziprasidone and zotepine)
- Carbidopa-levodopa (for Parkinson’s disease)

Tests

- Patients should be monitored for changes in blood pressure
- Although preliminary evidence from clinical trials suggests little or no weight gain, nonselective MAOIs are frequently associated with weight gain. Thus, before starting treatment for depression with high doses of selegiline, weigh all patients

and determine if the patient is already overweight (BMI 25.0–29.9) or obese (BMI ≥30)

- Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–125 mg/dL), diabetes (fasting plasma glucose >126 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment including nutrition and weight management, physical activity counseling, smoking cessation, and medical management

- Monitor weight and BMI during treatment
- While giving a drug to a patient who has gained >5% of initial weight, consider evaluating for the presence of pre-diabetes, diabetes, or dyslipidemia, or consider switching to a different antidepressant

SIDE EFFECTS

How Drug Causes Side Effects

- At recommended transdermal doses, norepinephrine, serotonin, and dopamine increase in parts of the brain and at receptors other than those that cause therapeutic actions
- At high transdermal doses, loss of tissue selectivity and loss of MAO-A sparing actions in the gut may enhance the possibility of dietary tyramine interactions if MAO-B inhibition occurs in the gut
- At recommended oral doses, dopamine increases in parts of the brain and body and at receptors other than those that cause therapeutic actions
- Side effects are generally immediate, but immediate side effects often disappear in time

Notable Side Effects

- Transdermal: application site reactions, headache, insomnia, diarrhea, dry mouth
- Oral: exacerbation of levodopa side effects, especially nausea, dizziness, abdominal pain, dry mouth, headache, dyskinesia, confusion, hallucinations, vivid dreams



Life-Threatening or Dangerous Side Effects

- Transdermal: hypertensive crisis was not observed with preliminary experience in clinical trials, even in patients who were not following a low tyramine diet
- Oral: hypertensive crisis (especially when MAOIs are used with certain tryamine-containing foods or prohibited drugs) – reduced risk at low oral doses compared to nonselective MAOIs
- Theoretically, when used at high doses may induce seizures and mania as do nonselective MAOIs
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Transdermal: reported but not expected; some patients may experience weight loss
- Oral: occurs in significant minority

Sedation



- Reported but not expected
- Can be activating in some patients

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- Switch after appropriate washout to an SSRI or newer antidepressant (depression)
- Switch to other antiparkinsonian therapies (Parkinson's disease)

Best Augmenting Agents for Side Effects

- Trazodone (with caution) for insomnia in depression
- Benzodiazepines for insomnia in depression
- Single oral or sublingual dose of a calcium channel blocker (e.g., nifedipine) for urgent treatment of hypertension due to drug interaction or dietary tyramine

- Many side effects cannot be improved with an augmenting agent, especially at lower doses

DOSING AND USE

Usual Dosage Range

- Depression (transdermal): 6 mg/24 hours–12 mg/24 hours
- Depression (oral): 30–60 mg/day
- Parkinson's disease/Alzheimer disease: 5–10 mg/day

Dosage Forms

- Transdermal patch 20 mg/20 cm² (6 mg/24 hours), 30 mg/30 cm² (9 mg/24 hours), 40 mg/40 cm² (12 mg/24 hours)
- Capsule 5 mg
- Tablet 5 mg scored
- Orally disintegrating tablet 1.25 mg

How to Dose

- Depression (transdermal): initial 6 mg/24 hours; can increase by 3 mg/24 hours every 2 weeks; maximum dose generally 12 mg/24 hours
- Parkinson's disease: initial 2.5 mg/day twice daily; increase to 5 mg twice daily; reduce dose of levodopa after 2–3 days



Dosing Tips

- Transdermal patch contains 1 mg of selegiline per 1 cm² and delivers approximately 0.3 mg of selegiline per cm² over 24 hours
- Patch is available in three sizes – 20 mg/20 cm², 30 mg/30 cm², and 40 mg/40 cm² – that deliver doses of approximately 6 mg, 9 mg, and 12 mg, respectively, over 24 hours
- At 6 mg/24 hours (transdermal) dietary adjustments are not generally required
- Dietary modifications to restrict tyramine intake from foods are recommended for doses above 6 mg/24 hours (transdermal)
- Transdermal patch should only be applied to dry, intact skin on the upper torso, upper thigh, or outer surface of the upper arm
- New application site should be selected for each day; patch should be applied at approximately the same time every day; only one patch should be applied at a time; patches should not be cut

- Avoid touching the exposed (sticky) side of the patch, and after application, wash hands with soap and water; do not touch eyes until after hands have been washed
- Heat could theoretically increase the amount of selegiline absorbed from the transdermal patch, so patients should avoid exposing the application site to external sources of direct heat (e.g., heating pads, prolonged direct sunlight)
- Although there is theoretically a 3-day reservoir of drug in each patch, multiday administration from a single patch is generally not recommended and has not been tested; because of residual drug in the patch after 24 hours of administration, discard used patches in a manner that prevents accidental application or ingestion by children, pets, or others
- For Parkinson's disease, oral dosage above 10 mg/day generally not recommended
- Dosage of carbidopa-levodopa can at times be reduced by 10–30% after 2–3 days of administering oral selegiline 5–10 mg/day in Parkinson's disease
- At doses above 10 mg/day (oral), selegiline may become nonselective and inhibit both MAO-A and MAO-B
- At doses above 30 mg/day (oral), selegiline may have antidepressant properties
- Patients receiving high oral doses may need to be evaluated periodically for effects on the liver
- Doses above 10 mg/day (oral) may increase the risk of hypertensive crisis, tyramine interactions, and drug interactions similar to those of phenelzine and tranylcypromine

Overdose

- Overdose with the transdermal formulation is likely to produce substantial amounts of MAO-A inhibition as well as MAO-B inhibition, and should be treated the same as overdose with a nonselective oral MAOI
- Dizziness, anxiety, ataxia, insomnia, sedation, irritability, headache; cardiovascular effects, confusion, respiratory depression, coma

Long-Term Use

- Long-term use has not been systematically studied although generally

recommended for chronic use as for other antidepressants

Habit Forming

- Lack of evidence for abuse potential with transdermal selegiline despite its metabolism to L-amphetamine and L-methamphetamine
- Some patients have developed dependence to other MAOIs

How to Stop

- Transdermal: MAOI slowly recovers over 2–3 weeks after patch removed
- Oral: generally no need to taper, as the drug wears off slowly over 2–3 weeks

Pharmacokinetics

- Clinical duration of action may be up to 14 days due to irreversible enzyme inhibition
- Major metabolite of selegiline is desmethylselegiline; other metabolites are L-methamphetamine and L-amphetamine
- Because first-pass metabolism is not extensive with transdermal dosing, this results in notably higher exposure to selegiline and lower exposure to metabolites as compared to oral dosing
- With transdermal selegiline, 25–30% of selegiline content is delivered systemically over 24 hours from each patch
- Mean half-life of transdermal selegiline is approximately 18–25 hours
- Steady-state mean elimination half-life of oral selegiline is approximately 10 hours



Drug Interactions

- Many misunderstandings about what drugs can be combined with MAOIs
- Theoretically and especially at high doses, selegiline could cause a fatal "serotonin syndrome" when combined with drugs that block serotonin reuptake, so do not use with a serotonin reuptake inhibitor for up to 5 half-lives after stopping the serotonin reuptake inhibitor (i.e., "wash-in" of selegiline should be about 1 week after discontinuing most agents [except 5 weeks or more after discontinuing fluoxetine because of its long half-life and that of its active metabolite]) (see Table 1 after Pearls)

- When discontinuing selegiline ("wash-out" period), wait 2 weeks before starting another antidepressant in order to allow enough time for the body to regenerate MAO enzyme
- Transdermal: no pharmacokinetic drug interactions present in studies with alprazolam, ibuprofen, levothyroxine, olanzapine, risperidone, and warfarin
- Tramadol may increase the risk of seizures in patients taking an MAOI
- Hypertensive crisis with headache, intracranial bleeding, and death may result from combining nonselective MAOIs with sympathomimetic drugs (e.g., amphetamines, methylphenidate, cocaine, dopamine, epinephrine, norepinephrine, and related compounds methyldopa, levodopa, L-tryptophan, L-tyrosine, and phenylalanine)
- Do not combine with another MAOI, alcohol, or guanethidine
- Adverse drug reactions can result from combining MAOIs with tricyclic/tetracyclic antidepressants and related compounds, including carbamazepine, cyclobenzaprine, and mirtazapine, and should be avoided except by experts to treat difficult cases
- Carbamazepine increases plasma levels of selegiline and is contraindicated with MAOIs
- MAOIs in combination with spinal anesthesia may cause combined hypotensive effects
- Combination of MAOIs and CNS depressants may enhance sedation and hypotension



Other Warnings/ Precautions

- Ingestion of a "high tyramine meal" is generally defined as 40 mg or more of tyramine in the fasted state
- Studies show that 200–400 mg of tyramine in the fasted state (and even more ingestion of tyramine in the fed state) may be required for a hypertensive response with administration of the low-dose transdermal patch (6 mg/24 hours); thus, no dietary precautions are required at this dose
- Tyramine sensitivity of the low-dose transdermal patch (6 mg/24 hours) may

be comparable to that of low-dose oral selegiline (10 mg) with neither causing a hypertensive reaction to high tyramine meals

- Tyramine sensitivity and hypertensive responses to the high-dose transdermal patch (12 mg/24 hours) may occur with administration of 70–100 mg of tyramine in the fasted state, so dietary restrictions may also not be necessary at 9 mg/24 hours or 12 mg/24 hours of transdermal administration of selegiline
- However, insufficient studies have been performed to be sure of the safety of transdermal administration at 9 mg/24 hours or 12 mg/24 hours, so dietary restrictions of tyramine are still recommended at these higher doses
- Oral administration of nonselective irreversible MAOIs generally requires adherence to a low tyramine diet (see Table 2 after Pearls)
- Ingestion of a "high tyramine meal" defined as 40 mg or more of tyramine in the fasted state or as little as ingestion of 10 mg of tyramine in the fasted state can cause hypertensive reactions in patients taking a nonselective irreversible MAOI orally
- Food restrictions (see Table 2 after Pearls) are generally recommended for patients taking the higher doses of transdermal selegiline (9 mg/24 hours or 12 mg/24 hours) but not for the lower doses of transdermal selegiline (6 mg/24 hours) or for the low dose orally (10 mg)
- Transdermal: studies of low-dose transdermal administration of selegiline (6 mg/24 hours) failed to show changes in systolic or diastolic blood pressure or pulse when administered to normal volunteers taking either pseudoephedrine 60 mg three times a day for 2 days or 25 mg of phenylpropanolamine (no longer commercially available in the USA) every 4 hours for 1 day
- However, sufficient safety information is not available to recommend administration of pseudoephedrine without a precaution; blood pressure should be monitored if low-dose transdermal selegiline is given at all with pseudoephedrine
- Pseudoephedrine may need to be avoided when administering transdermal selegiline,

particularly at higher doses of selegiline or in vulnerable patients with hypertension

- Although risk may be reduced with transdermal administration of selegiline, patient and prescriber must be vigilant to potential interactions with any drug, including antihypertensives and over-the-counter cough/cold preparations
- Over-the-counter medications to avoid or use with caution under the care of an expert include cough and cold preparations, including those containing dextromethorphan, nasal decongestants (tablets, drops, or spray), hay-fever medications, sinus medications, asthma inhalant medications, anti-appetite medications, weight reducing preparations, "pep" pills (see Table 3 after Pearls)
- Certain transdermal patches containing even small traces of aluminum or other metals in the adhesive backing can cause skin burns if worn during MRI, so warn patients taking the transdermal formulation about this possibility and advise them to disclose this information if they need an MRI
- Hypoglycemia may occur in diabetic patients receiving insulin or oral antidiabetic agents
- Use cautiously in patients receiving reserpine, anesthetics, disulfiram, metrizamide, anticholinergic agents
- Selegiline is not recommended for use in patients who cannot be monitored closely
- Only use sympathomimetic agents or guanethidine with oral doses of selegiline below 10 mg/day
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is taking meperidine (pethidine)
- If patient is taking a sympathomimetic agent or taking guanethidine
- If patient is taking another MAOI
- If patient is taking any agent that can inhibit serotonin reuptake (e.g., SSRIs, sibutramine, tramadol, milnacipran, duloxetine, venlafaxine, clomipramine, etc.)
- If patient is taking diuretics, dextromethorphan
- If patient is taking St. John's wort, cyclobenzaprine, methadone, propoxyphene
- If patient has pheochromocytoma
- If patient is undergoing elective surgery and requires general anesthesia
- If there is a proven allergy to selegiline

SPECIAL POPULATIONS

Renal Impairment

- No dose adjustment necessary for transdermal administration in patients with mild to moderate renal impairment
- Use oral administration with caution – drug may accumulate in plasma in patients with renal impairment
- Oral administration may require lower than usual adult dose

Hepatic Impairment

- No dose adjustment necessary for transdermal administration in patients with mild to moderate hepatic impairment
- Oral administration may require lower than usual adult dose

Cardiac Impairment

- May require lower than usual adult dose
- Observe closely for orthostatic hypotension

Elderly

- Recommended dose for patients over 65 years old is 20 mg oral and 6 mg/day transdermal
- Dose increases in the elderly should be made with caution and patients should be observed for postural changes in blood pressure throughout treatment
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Not recommended for use in children under 18
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester
- Should evaluate patient for treatment with an antidepressant with a better risk/benefit ratio

Breast Feeding

- Some drug is found in mother's breast milk
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Should evaluate patient for treatment with an antidepressant with a better risk/benefit ratio

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Treatment-resistant depression
- Patients with atypical depression (hypersomnia, hyperphagia)
- Patients who wish to avoid weight gain and sexual dysfunction
- Parkinson's patients inadequately responsive to levodopa

Potential Disadvantages

- Noncompliant patients
- Patients with motor complications and fluctuations on levodopa treatment
- Patients with cardiac problems or hypertension

Primary Target Symptoms

- Depressed mood (depression)
- Somatic symptoms (depression)
- Sleep and eating disturbances (depression)
- Psychomotor disturbances (depression)
- Motor symptoms (Parkinson's disease)



Pearls

- Transdermal administration may allow freedom from dietary restrictions
- Transdermal selegiline theoretically appealing as a triple action agent (serotonin, norepinephrine, and dopamine) for treatment-refractory and difficult cases of depression
- Transdermal selegiline may have low risk of weight gain and sexual dysfunction, and may be useful for cognitive dysfunction in attention deficit disorder and other cognitive disorders, as it increases dopamine and is metabolized to L-amphetamine and L-methamphetamine
- Low-dose oral administration generally used as an adjunctive treatment for Parkinson's disease after other drugs have lost efficacy
- At oral doses used for Parkinson's disease, virtually no risk of interactions with food
- Neuroprotective effects are possible but unproved
- Enhancement of levodopa action can occur for Parkinson's patients at low oral doses, but antidepressant actions probably require high oral doses that do not have the potential tissue selectivity and lack

SELEGILINE (continued)

of dietary restrictions of the low-dose transdermal formulation

- ✿ High doses may lose safety features
- MAOIs are generally reserved for second-line use after SSRIs, SNRIs, and combinations of newer antidepressants have failed
- Patient should be advised not to take any prescription or over-the-counter drugs without consulting their doctor because of possible drug interactions
- Headache is often the first symptom of hypertensive crisis

- Myths about the danger of dietary tyramine can be exaggerated, but prohibitions against concomitant drugs often not followed closely enough

- ✿ Combining multiple psychotropic agents with MAOIs should be for the expert, especially if combining with agents of potential risk (e.g., stimulants, trazodone, TCAs)

- ✿ MAOIs should not be neglected as therapeutic agents for the treatment-resistant

Table 1. Drugs contraindicated due to risk of serotonin syndrome/toxicity

Do Not Use:			
Antidepressants	Drugs of Abuse	Opioids	Other
SSRIs	MDMA (ecstasy)	Meperidine	Non-subcutaneous sumatriptan
SNRIs	Cocaine	Tramadol	Chlorpheniramine
Clomipramine	Methamphetamine	Methadone	Brompheniramine
St. John's wort	High-dose or injected amphetamine	Fentanyl	Dextromethorphan
			Procarbazine?

Table 2. Dietary guidelines for patients taking MAOIs

Foods to avoid*	Foods allowed
Dried, aged, smoked, fermented, spoiled, or improperly stored meat, poultry, and fish	Fresh or processed meat, poultry, and fish; properly stored pickled or smoked fish
Broad bean pods	All other vegetables
Aged cheeses	Processed cheese slices, cottage cheese, ricotta cheese, yogurt, cream cheese
Tap and unpasteurized beer	Canned or bottled beer and alcohol
Marmite	Brewer's and baker's yeast
Sauerkraut, kimchee	
Soy products/tofu	Peanuts
Banana peel	Bananas, avocados, raspberries
Tyramine-containing nutritional supplement	

*Not necessary for 6-mg transdermal or low-dose oral selegiline

Table 3. Drugs that boost norepinephrine: should only be used with caution with MAOIs

Use With Caution:			
Decongestants	Stimulants	Antidepressants with norepinephrine reuptake inhibition	Other
Phenylephrine	Amphetamines	Most tricyclics	Phentermine
Pseudoephedrine	Methylphenidate	NRIs	Local anesthetics containing vasoconstrictors
	Cocaine	NDRIs	
	Methamphetamine		
	Modafinil		Tapentadol
	Armodafinil		



Suggested Reading

Bodkin JA, Amsterdam JD. Transdermal selegiline in major depression: a double-blind, placebo-controlled, parallel-group study in outpatients. *Am J Psychiatry* 2002;159(11):1869–75.

Kennedy SH. Continuation and maintenance treatments in major depression: the neglected

role of monoamine oxidase inhibitors. *J Psychiatry Neurosci* 1997;22:127–31.

Shulman KI, Walker SE. A reevaluation of dietary restrictions for irreversible monoamine oxidase inhibitors. *Psychiatr Ann* 2001;31:378–84.

THERAPEUTICS

Brands • SERDOLECT

see index for additional brand names

Generic? No**Class**

- Neuroscience-based Nomenclature: dopamine and serotonin receptor antagonist (DS-RAN)
- Atypical antipsychotic (serotonin-dopamine antagonist; second-generation antipsychotics; also a mood stabilizer)

Commonly Prescribed for

(bold for FDA approved)

- Schizophrenia (for patients intolerant to at least one other antipsychotic)
- Acute mania/mixed mania
- Other psychotic disorders
- Bipolar maintenance
- Bipolar depression
- Treatment-resistant depression

**How the Drug Works**

- Blocks dopamine 2 receptors, reducing positive symptoms of psychosis and stabilizing affective symptoms
- Blocks serotonin 2A receptors, causing enhancement of dopamine release in certain brain regions and thus reducing motor side effects and possibly improving cognitive and affective symptoms

✳ Serotonin 2C properties may contribute to antidepressant actions

How Long Until It Works

- Psychotic symptoms can improve within 1 week, but it may take several weeks for full effect on behavior as well as on cognition
- Classically recommended to wait at least 4–6 weeks to determine efficacy of drug, but in practice some patients may require up to 16–20 weeks to show a good response, especially on cognitive symptoms

If It Works

- Most often reduces positive symptoms but does not eliminate them
- Can improve negative symptoms, as well as aggressive, cognitive, and affective symptoms in schizophrenia

- Most schizophrenia patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third
- Perhaps 5–15% of schizophrenia patients can experience an overall improvement of greater than 50–60%, especially when receiving stable treatment for more than a year
- Such patients are considered super-responders or “awakeners” since they may be well enough to be employed, live independently, and sustain long-term relationships
- Continue treatment until reaching a plateau of improvement
- After reaching a satisfactory plateau, continue treatment for at least a year after first episode of psychosis
- For second and subsequent episodes of psychosis, treatment may need to be indefinite
- Even for first episodes of psychosis, it may be preferable to continue treatment

If It Doesn't Work

- Try one of the other atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, iloperidone, asenapine, amisulpride, lurasidone)
- If 2 or more antipsychotic monotherapies do not work, consider clozapine
- Some patients may require treatment with a conventional antipsychotic
- If no first-line atypical antipsychotic is effective, consider higher doses or augmentation with valproate or lamotrigine
- Consider noncompliance and switch to another antipsychotic with fewer side effects or to an antipsychotic that can be given by depot injection
- Consider initiating rehabilitation and psychotherapy such as cognitive remediation
- Consider presence of concomitant drug abuse

**Best Augmenting Combos for Partial Response or Treatment Resistance**

- Valproic acid (valproate, divalproex, divalproex ER)
- Other mood-stabilizing anticonvulsants (carbamazepine, oxcarbazepine, lamotrigine)
- Lithium
- Benzodiazepines

Tests

- Baseline EKG, serum potassium, and serum magnesium measurements
- EKG should be repeated upon reaching steady state about 3 weeks after treatment initiation or upon reaching 16 mg/day, at 3 months, and then every 3 months for the duration of treatment
- EKG is recommended prior to and after any dose increase as well as after addition of any drug that can change sertindole concentration (e.g., CYP450 2D6 or 3A4 inhibitors)

Before starting an atypical antipsychotic

- ✖ Weigh all patients and track BMI during treatment
- Get baseline personal and family history of diabetes, obesity, dyslipidemia, hypertension, and cardiovascular disease
- ✖ Get waist circumference (at umbilicus), blood pressure, fasting plasma glucose, and fasting lipid profile
- Determine if the patient is
 - overweight (BMI 25.0–29.9)
 - obese (BMI >30)
 - has pre-diabetes (fasting plasma glucose 100–125 mg/dL)
 - has diabetes (fasting plasma glucose >126 mg/dL)
 - has hypertension (BP >140/90 mm Hg)
 - has dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol)
- Treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management

Monitoring after starting an atypical antipsychotic

- ✖ BMI monthly for 3 months, then quarterly
- ✖ Consider monitoring fasting triglycerides monthly for several months in patients at high risk for metabolic complications and when initiating or switching antipsychotics
- ✖ Blood pressure, fasting plasma glucose, fasting lipids within 3 months and then annually, but earlier and more frequently for patients with diabetes or who have gained >5% of initial weight
- Treat or refer for treatment and consider switching to another atypical antipsychotic for patients who become overweight, obese, pre-diabetic, diabetic, hypertensive,

or dyslipidemic while receiving an atypical antipsychotic

- ✖ Even in patients without known diabetes, be vigilant for the rare but life-threatening onset of diabetic ketoacidosis, which always requires immediate treatment, by monitoring for the rapid onset of polyuria, polydipsia, weight loss, nausea, vomiting, dehydration, rapid respiration, weakness, and clouding of sensorium, even coma
- Should check blood pressure during titration and early maintenance treatment

SIDE EFFECTS

How Drug Causes Side Effects

- By blocking alpha 1 adrenergic receptors, it can cause dizziness, sedation, and hypotension
- By blocking dopamine 2 receptors in the striatum, it can cause motor side effects
- By blocking dopamine 2 receptors in the pituitary, it can cause elevations in prolactin
- Mechanism of weight gain and increased incidence of diabetes and dyslipidemia with atypical antipsychotics is unknown

Notable Side Effects

- ✖ Orthostatic hypotension
- Dizziness, dry mouth, nasal congestion
- Weight gain, peripheral edema, decreased ejaculatory volume
- ✖ May increase risk for diabetes and dyslipidemia
- Rare tardive dyskinesia (much reduced risk compared to conventional antipsychotics)



Life-Threatening or Dangerous Side Effects

- Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking atypical antipsychotics
- Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis
- Rare neuroleptic malignant syndrome (much reduced risk compared to conventional antipsychotics)
- Rare seizures

Weight Gain



- Many experience and/or can be significant in amount
- May be less than for some antipsychotics, more than for others

Sedation



- Reported but not expected

What to Do About Side Effects

- Wait
- Wait
- Wait
- Anticholinergics may reduce motor side effects when present
- Weight loss, exercise programs, and medical management for high BMIs, diabetes, dyslipidemia
- Switch to another atypical antipsychotic

Best Augmenting Agents for Side Effects

- Benztrapine or trihexyphenidyl for motor side effects
- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 12–20 mg/day

Dosage Forms

- Tablet 4 mg, 12 mg, 16 mg, 20 mg

How to Dose

- Initial 4 mg/day; increase by 4 mg every 4–5 days; maximum dose generally 24 mg/day



Dosing Tips

- A starting dose of 8 mg or a rapid increase in dose significantly increase risk of orthostatic hypotension
- Sertindole should be discontinued if QTc interval of more than 500 msec is observed during treatment

Overdose

- Fatalities have been reported; sedation, slurred speech, tachycardia, hypotension, transient QTc prolongation; torsade de pointes

Long-Term Use

- Not studied, but long-term maintenance treatment is often necessary for schizophrenia

Habit Forming

- No

How to Stop

- Down-titration, especially when simultaneously beginning a new antipsychotic while switching (i.e., cross-titration)
- Rapid discontinuation could theoretically lead to rebound psychosis and worsening of symptoms

Pharmacokinetics

- Terminal half-life approximately 3 days
- Extensively metabolized by CYP450 2D6 and 3A



Drug Interactions

- May increase effects of antihypertensive agents
- May antagonize levodopa, dopamine agonists
- May enhance QTc prolongation of other drugs capable of prolonging QTc interval
- Inhibitors of CYP450 2D6 (e.g., paroxetine, fluoxetine, duloxetine, quinidine) may significantly increase plasma levels of sertindole and require a dosage reduction of sertindole
- Inhibitors of CYP450 3A (e.g., nefazodone, fluvoxamine, fluoxetine, ketoconazole) can increase plasma levels of sertindole and concomitant use of these agents with sertindole is contraindicated



Other Warnings/ Precautions

- Use with caution in patients with conditions that predispose to hypotension (dehydration, overheating)
- Dysphagia has been associated with antipsychotic use, and sertindole should

be used cautiously in patients at risk for aspiration pneumonia

- Sertindole prolongs QTc interval more than some other antipsychotics

Do Not Use

- If patient is taking agents capable of significantly prolonging QTc interval (e.g., pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin)
- If there is a personal or family history of QTc prolongation
- If there is a history of significant cardiovascular illness, including congestive heart failure, cardiac hypertrophy, arrhythmia, bradycardia, or congenital prolonged QT syndrome
- If patient has hypokalemia, hypomagnesemia, or QTc greater than 450 msec (males) or 470 msec (females)
- If patient is taking a CYP450 3A inhibitor
- If patient has severe hepatic impairment
- If patient has galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption
- If there is a proven allergy to sertindole

SPECIAL POPULATIONS

Renal Impairment

- Dose adjustment not generally necessary

Hepatic Impairment

- For mild to moderate impairment, use slower titration and lower maintenance dose
- Contraindicated in patients with severe hepatic impairment

Cardiac Impairment

- Drug should be used with caution because of risk of orthostatic hypotension
- Not recommended for patients with significant cardiovascular illness, including congestive heart failure, cardiac hypertrophy, arrhythmia, bradycardia, or congenital prolonged QT syndrome

Elderly

- Use cautiously and only after thorough cardiovascular examination
- Some patients may tolerate lower doses better

- Although atypical antipsychotics are commonly used for behavioral disturbances in dementia, no agent has been approved for treatment of elderly patients with dementia-related psychosis
- Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo, and also have an increased risk of cerebrovascular events



Children and Adolescents

- Safety and efficacy have not been established
- Children and adolescents using sertindole may need to be monitored more often than adults



Pregnancy

- Some animal studies show adverse effects; no controlled studies in humans
- There is a risk of abnormal muscle movements and withdrawal symptoms in newborns whose mothers took an antipsychotic during the third trimester; symptoms may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty feeding
- Psychotic symptoms may worsen during pregnancy and some form of treatment may be necessary

Breast Feeding

- Unknown if sertindole is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- Recommended either to discontinue drug or bottle feed
- Infants of women who choose to breast feed while on sertindole should be monitored for possible adverse effects

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Some cases of psychosis and bipolar disorder refractory to treatment with other antipsychotics

Potential Disadvantages

- Patients requiring rapid onset of antipsychotic action without dosage titration

Primary Target Symptoms

- Positive symptoms of psychosis
- Negative symptoms of psychosis
- Cognitive symptoms
- Unstable mood (both depression and mania)
- Aggressive symptoms



Pearls

- Aimed at patients intolerant to at least one other antipsychotic and when potential benefits outweigh potential risks

- Not approved for mania, but all atypical antipsychotics approved for acute schizophrenia are generally also useful for acute bipolar mania
- Not approved for depression, but binding properties suggest potential use in treatment-resistant and bipolar depression, though probably not as a first- or second-line agent given the need to accumulate more real-world clinical experience of any actual risks of sertindole



Suggested Reading

Komossa K, Rummel-Kluge C, Hunger H, et al. Sertindole versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev 2009;2:CD006752.

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THERAPEUTICS

Brands • Zoloft

see index for additional brand names

Generic? Yes**Class**

- Neuroscience-based Nomenclature: serotonin reuptake inhibitor (S-RI)
- SSRI (selective serotonin reuptake inhibitor); often classified as an antidepressant, but it is not just an antidepressant

Commonly Prescribed for

(bold for FDA approved)

- Major depressive disorder
- Premenstrual dysphoric disorder (PMDD)
- Panic disorder
- Posttraumatic stress disorder (PTSD)
- Social anxiety disorder (social phobia)
- Obsessive-compulsive disorder (OCD)
- Generalized anxiety disorder (GAD)

**How the Drug Works**

- Boosts neurotransmitter serotonin
- Blocks serotonin reuptake pump (serotonin transporter)
- Desensitizes serotonin receptors, especially serotonin 1A receptors
- Presumably increases serotonergic neurotransmission
- Sertraline also has some ability to block dopamine reuptake pump (dopamine transporter), which could increase dopamine neurotransmission and contribute to its therapeutic actions
- Sertraline also binds at sigma 1 receptors

How Long Until It Works

- Some patients may experience increased energy or activation early after initiation of treatment
- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
 - If it is not working within 6–8 weeks, it may require a dosage increase or it may not work at all
 - May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Continue treatment until all symptoms are gone (remission) or significantly reduced (e.g., OCD, PTSD)
- Once symptoms are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders may also need to be indefinite

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating in depression)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some patients who have an initial response may relapse even though they continue treatment, sometimes called “poop-out”
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer

**Best Augmenting Combos for Partial Response or Treatment Resistance**

- Trazodone, especially for insomnia
- In the USA, sertraline (Zoloft) is commonly augmented with bupropion (Wellbutrin) with good results in a combination anecdotally called “Well-loft” (use combinations of antidepressants with caution as this may activate bipolar disorder and suicidal ideation)

- Mirtazapine, reboxetine, or atomoxetine (add with caution and at lower doses since sertraline could theoretically raise atomoxetine levels); use combinations of antidepressants with caution as this may activate bipolar disorder and suicidal ideation
- Modafinil, especially for fatigue, sleepiness, and lack of concentration
- Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression, treatment-resistant depression, or treatment-resistant anxiety disorders
- Benzodiazepines
- If all else fails for anxiety disorders, consider gabapentin or tiagabine
- Hypnotics for insomnia
- Classically, lithium, buspirone, or thyroid hormone

Tests

- None for healthy individuals

SIDE EFFECTS

How Drug Causes Side Effects

- Theoretically due to increases in serotonin concentrations at serotonin receptors in parts of the brain and body other than those that cause therapeutic actions (e.g., unwanted actions of serotonin in sleep centers causing insomnia, unwanted actions of serotonin in the gut causing diarrhea, etc.)
- Increasing serotonin can cause diminished dopamine release and might contribute to emotional flattening, cognitive slowing, and apathy in some patients, although this could theoretically be diminished in some patients by sertraline's dopamine reuptake blocking properties
- Most side effects are immediate but often go away with time, in contrast to most therapeutic effects which are delayed and are enhanced over time
- Sertraline's possible dopamine reuptake blocking properties could contribute to agitation, anxiety, and undesirable activation, especially early in dosing

Notable Side Effects

- Sexual dysfunction (dose-dependent; men: delayed ejaculation, erectile dysfunction;

men and women: decreased sexual desire, anorgasmia)

- Gastrointestinal (decreased appetite, nausea, diarrhea, constipation, dry mouth)
- Mostly CNS (insomnia but also sedation, agitation, tremors, headache, dizziness)
- Note: patients with diagnosed or undiagnosed bipolar or psychotic disorders may be more vulnerable to CNS-activating actions of SSRIs
- Autonomic (sweating)
- Bruising and rare bleeding
- Rare hyponatremia (mostly in elderly patients and generally reversible on discontinuation of sertraline)
- Rare hypotension
- SIADH (syndrome of inappropriate antidiuretic hormone secretion)



Life-Threatening or Dangerous Side Effects

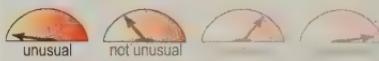
- Rare seizures
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Reported but not expected
- Some patients may actually experience weight loss

Sedation



- Reported but not expected
- Possibly activating in some patients

What to Do About Side Effects

- Wait
- Wait
- Wait
- If sertraline is activating, take in the morning to help reduce insomnia
- Reduce dose to 25 mg or even 12.5 mg until side effects abate, then increase dose as tolerated, usually to at least 50 mg/day
- In a few weeks, switch or add other drugs

Best Augmenting Agents for Side Effects

- Often best to try another SSRI or another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
- Trazodone or a hypnotic for insomnia
- Bupropion, sildenafil, vardenafil, or tadalafil for sexual dysfunction
- Bupropion for emotional flattening, cognitive slowing, or apathy
- Mirtazapine for insomnia, agitation, and gastrointestinal side effects
- Benzodiazepines for jitteriness and anxiety, especially at initiation of treatment and especially for anxious patients
- Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of sertraline

DOSING AND USE

Usual Dosage Range

- 50–200 mg/day

Dosage Forms

- Tablets 25 mg scored, 50 mg scored, 100 mg
- Oral solution 20 mg/mL

How to Dose

- Depression and OCD: initial 50 mg/day; usually wait a few weeks to assess drug effects before increasing dose, but can increase once a week; maximum generally 200 mg/day; single dose
- Panic, PTSD, and social anxiety: initial 25 mg/day; increase to 50 mg/day after 1 week thereafter, usually wait a few weeks to assess drug effects before increasing

dose; maximum generally 200 mg/day; single dose

- PMDD: initial 50 mg/day; can dose daily through the menstrual cycle or limit to the luteal phase
- Oral solution: mix with 4 oz of water, ginger ale, lemon/lime soda, lemonade, or orange juice only; drink immediately after mixing



Dosing Tips

- All tablets are scored, so to save costs, give 50 mg as half of 100-mg tablet, since 100-mg and 50-mg tablets cost about the same in many markets
- Give once daily, often in the mornings to reduce chances of insomnia
- Many patients ultimately require more than 50 mg dose per day
- Some patients are dosed above 200 mg
- Evidence that some treatment-resistant OCD patients may respond safely to doses up to 400 mg/day, but this is for experts and use with caution
- The more anxious and agitated the patient, the lower the starting dose, the slower the titration, and the more likely the need for a concomitant agent such as trazodone or a benzodiazepine
- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar disorder and switch to a mood stabilizer or atypical antipsychotic
- Utilize half a 25-mg tablet (12.5 mg) when initiating treatment in patients with a history of intolerance to previous antidepressants

Overdose

- Rarely lethal in monotherapy overdose; vomiting, sedation, heart rhythm disturbances, dilated pupils, agitation; fatalities have been reported in sertraline overdose combined with other drugs or alcohol

Long-Term Use

- Safe

Habit Forming

- No

How to Stop

- Taper to avoid withdrawal effects (dizziness, nausea, stomach cramps, sweating, tingling, dysesthesias)
- Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation
- If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly

Pharmacokinetics

- Parent drug has 22–36 hour half-life
- Metabolite half-life 62–104 hours
- Inhibits CYP450 2D6 (weakly at low doses)
- Inhibits CYP450 3A4 (weakly at low doses)



Drug Interactions

- Tramadol increases the risk of seizures in patients taking an antidepressant
- Can increase TCA levels; use with caution with TCAs or when switching from a TCA to sertraline
- Can cause a fatal “serotonin syndrome” when combined with MAOIs, so do not use with MAOIs or for at least 14 days after MAOIs are stopped
- Do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing sertraline
- May displace highly protein bound drugs (e.g., warfarin)
- Can rarely cause weakness, hyperreflexia, and incoordination when combined with sumatriptan or possibly with other triptans, requiring careful monitoring of patient
- Possible increased risk of bleeding, especially when combined with anticoagulants (e.g., warfarin, NSAIDs)
- NSAIDs may impair effectiveness of SSRIs
- Via CYP450 2D6 inhibition, sertraline could theoretically interfere with the analgesic actions of codeine, and increase the plasma levels of some beta blockers and of atomoxetine
- Via CYP450 2D6 inhibition sertraline could theoretically increase concentrations of thioridazine and cause dangerous cardiac arrhythmias

- Via CYP450 3A4 inhibition, sertraline may increase the levels of alprazolam, buspirone, and triazolam
- Via CYP450 3A4 inhibition, sertraline could theoretically increase concentrations of certain cholesterol lowering HMG CoA reductase inhibitors, especially simvastatin, atorvastatin, and lovastatin, but not pravastatin or fluvastatin, which would increase the risk of rhabdomyolysis; thus, coadministration of sertraline with certain HMG CoA reductase inhibitors should proceed with caution
- Via CYP450 3A4 inhibition, sertraline could theoretically increase the concentrations of pimozide, and cause QTc prolongation and dangerous cardiac arrhythmias
- Via CYP450 3A4 inhibition, sertraline could theoretically increase the concentrations of pimozide, and cause QTc prolongation and dangerous cardiac arrhythmias
- False-positive urine immunoassay screening tests for benzodiazepine have been reported in patients taking sertraline due to a lack of specificity of the screening tests. False-positive results may be expected for several days following discontinuation of sertraline



Other Warnings/ Precautions

- Add or initiate other antidepressants with caution for up to 2 weeks after discontinuing sertraline
- Use with caution in patients with history of seizures
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is taking an MAOI
- If patient is taking pimozide
- If patient is taking thioridazine
- Use of sertraline oral concentrate is contraindicated with disulfiram due to the alcohol content of the concentrate
- If there is a proven allergy to sertraline

SPECIAL POPULATIONS

Renal Impairment

- No dose adjustment
- Not removed by hemodialysis

Hepatic Impairment

- Lower dose or give less frequently, perhaps by half

Cardiac Impairment

- Proven cardiovascular safety in depressed patients with recent myocardial infarction or angina
- Treating depression with SSRIs in patients with acute angina or following myocardial infarction may reduce cardiac events and improve survival as well as mood

Elderly

- Some patients may tolerate lower doses and/or slower titration better
- Risk of SIADH with SSRIs is higher in the elderly
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients

- Approved for use in OCD
- Ages 6–12: initial dose 25 mg/day
- Ages 13 and up: adult dosing
- Long-term effects, particularly on growth, have not been studied



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester
- Nonetheless, continuous treatment during pregnancy may be necessary and has not been proven to be harmful to the fetus
- At delivery there may be more bleeding in the mother and transient irritability or sedation in the newborn
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy
- Exposure to SSRIs early in pregnancy may be associated with increased risk of septal heart defects (absolute risk is small)
- SSRI use beyond the 20th week of pregnancy may be associated with increased risk of pulmonary hypertension in newborns, although this is not proven
- Exposure to SSRIs late in pregnancy may be associated with increased risk of gestational hypertension and preeclampsia
- Neonates exposed to SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding; reported symptoms are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome, and

include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying

Breast Feeding

- Some drug is found in mother's breast milk
- Trace amounts may be present in nursing children whose mothers are on sertraline
- Sertraline has shown efficacy in treating postpartum depression
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients, this may mean continuing treatment during breast feeding

Primary Target Symptoms

- Depressed mood
- Anxiety
- Sleep disturbance, both insomnia and hypersomnia (eventually, but may actually cause insomnia, especially short-term)
- Panic attacks, avoidant behavior, re-experiencing, hyperarousal



Pearls

- ✿ May be a type of "dual action" agent with both potent serotonin reuptake inhibition and less potent dopamine reuptake inhibition, but the clinical significance of this is unknown
- Cognitive and affective "flattening" may theoretically be diminished in some patients by sertraline's dopamine reuptake blocking properties
- ✿ May be a first-line choice for atypical depression (e.g., hypersomnia, hyperphagia, low energy, mood reactivity)
- Best documented cardiovascular safety of any antidepressant, proven safe for depressed patients with recent myocardial infarction or angina
- May bind to sigma 1 receptors, enhancing sertraline's anxiolytic actions
- Can have more gastrointestinal effects, particularly diarrhea, than some other antidepressants
- May be more effective treatment for women with PTSD or depression than for men with PTSD or depression, but the clinical significance of this is unknown
- SSRIs may be less effective in women over 50, especially if they are not taking estrogen
- SSRIs may be useful for hot flushes in perimenopausal women
- For sexual dysfunction, can augment with bupropion, sildenafil, vardenafil, tadalafil, or switch to a non-SSRI such as bupropion or mirtazapine
- Some postmenopausal women's depression will respond better to sertraline plus estrogen augmentation than to sertraline alone
- Nonresponse to sertraline in elderly may require consideration of mild cognitive impairment or Alzheimer disease
- Not as well tolerated as some SSRIs for panic, especially when dosing is initiated,

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients with atypical depression (hypersomnia, increased appetite)
- Patients with fatigue and low energy
- Patients who wish to avoid hyperprolactinemia (e.g., pubescent children, girls and women with galactorrhea, girls and women with unexplained amenorrhea, postmenopausal women who are not taking estrogen replacement therapy)
- Patients who are sensitive to the prolactin-elevating properties of other SSRIs (sertraline is the one SSRI that generally does not elevate prolactin)

Potential Disadvantages

- Initiating treatment in anxious patients with some insomnia
- Patients with comorbid irritable bowel syndrome
- Can require dosage titration

unless given with co-therapies such as benzodiazepines or trazodone

- Relative lack of effect on prolactin may make it a preferred agent for some children, adolescents, and women

- Some evidence suggests that sertraline treatment during only the luteal phase may be more effective than continuous treatment for patients with PMDD

Suggested Reading

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Flament MF, Lane RM, Zhu R, Ying Z. Predictors of an acute antidepressant response to fluoxetine and sertraline. *Int Clin Psychopharmacol* 1999;14:259–75.

Khouzam HR, Emes R, Gill T, Raroque R. The antidepressant sertraline: a review of its uses in a range of psychiatric and medical conditions. *Compr Ther* 2003;29:47–53.

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THERAPEUTICS

Brands • Dolmatil

see index for additional brand names

Generic? Yes**Class**

- Neuroscience-based Nomenclature: dopamine receptor antagonist (D-RAn)
- Conventional antipsychotic (neuroleptic, benzamide, dopamine 2 antagonist)

Commonly Prescribed for

(bold for FDA approved)

- Schizophrenia
- Depression

**How the Drug Works**

- Blocks dopamine 2 receptors, reducing positive symptoms of psychosis
- Blocks dopamine 3 and 4 receptors, which may contribute to sulpiride's actions
- ✿ Possibly blocks presynaptic dopamine 2 autoreceptors more potently at low doses, which could theoretically contribute to improving negative symptoms of schizophrenia as well as depression

How Long Until It Works

- Psychotic symptoms can improve within 1 week, but it may take several weeks for full effect on behavior

If It Works

- Most often reduces positive symptoms in schizophrenia but does not eliminate them
- Most schizophrenic patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third
- Continue treatment in schizophrenia until reaching a plateau of improvement
- After reaching a satisfactory plateau, continue treatment for at least a year after first episode of psychosis in schizophrenia
- For second and subsequent episodes of psychosis in schizophrenia, treatment may need to be indefinite

If It Doesn't Work

- Consider trying one of the first-line atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole,

paliperidone, amisulpride, asenapine, iloperidone, lurasidone)

- Consider trying another conventional antipsychotic
- If 2 or more antipsychotic monotherapies do not work, consider clozapine

**Best Augmenting Combos for Partial Response or Treatment Resistance**

- Augmentation of conventional antipsychotics has not been systematically studied
- Addition of a mood-stabilizing anticonvulsant such as valproate, carbamazepine, or lamotrigine may be helpful in both schizophrenia and bipolar mania
- Augmentation with lithium in bipolar mania may be helpful
- Addition of a benzodiazepine, especially short-term for agitation

Tests

- ✿ Since conventional antipsychotics are frequently associated with weight gain, before starting treatment, weigh all patients and determine if the patient is already overweight (BMI 25.0–29.9) or obese (BMI ≥30)
- Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–125 mg/dL), diabetes (fasting plasma glucose >126 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management
- ✿ Consider monitoring fasting triglycerides monthly for several months in patients at high risk for metabolic complications and when initiating or switching antipsychotics
- ✿ Monitor weight and BMI during treatment
- ✿ While giving a drug to a patient who has gained >5% of initial weight, consider evaluating for the presence of pre-diabetes, diabetes, or dyslipidemia, or consider switching to a different antipsychotic
- Monitoring elevated prolactin levels of dubious clinical benefit
- Patients with low white blood cell count (WBC) or history of drug-induced

SULPIRIDE (continued)

leucopenia/neutropenia should have complete blood count (CBC) monitored frequently during the first few months and sulpiride should be discontinued at the first sign of decline of WBC in the absence of other causative factors

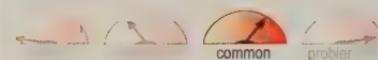
- Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis

Weight Gain



- Many experience and/or can be significant in amount

Sedation



- Many experience and/or can be significant in amount, especially at high doses

What to Do About Side Effects

- Wait
- Wait
- Wait
- For motor symptoms, add an anticholinergic agent
- Reduce the dose
- For sedation, give at night
- Switch to an atypical antipsychotic
- Weight loss, exercise programs, and medical management for high BMIs, diabetes, dyslipidemia

Best Augmenting Agents for Side Effects

- Benztropine or trihexyphenidyl for motor side effects
- Sometimes amantadine can be helpful for motor side effects
- Benzodiazepines may be helpful for akathisia
- Many side effects cannot be improved with an augmenting agent

Sulpiride SIDE EFFECTS

How Drug Causes Side Effects

- By blocking dopamine 2 receptors in the striatum, it can cause motor side effects
- By blocking dopamine 2 receptors in the pituitary, it can cause elevations in prolactin
- By blocking dopamine 2 receptors excessively in the mesocortical and mesolimbic dopamine pathways, especially at high doses, it can cause worsening of negative and cognitive symptoms (neuroleptic-induced deficit syndrome)
- Anticholinergic actions may cause sedation, blurred vision, constipation, dry mouth
- Antihistaminic actions may cause sedation, weight gain
- By blocking alpha 1 adrenergic receptors, it can cause dizziness, sedation, and hypotension
- Mechanism of weight gain and any possible increased incidence of diabetes or dyslipidemia with conventional antipsychotics is unknown

Notable Side Effects

- Extrapyramidal symptoms, akathisia
- Prolactin elevation, galactorrhea, amenorrhea
- Sedation, dizziness, sleep disturbance, headache, impaired concentration
- Dry mouth, nausea, vomiting, constipation, anorexia
- Impotence
- Rare tardive dyskinesia
- Rare hypomania
- Palpitations, hypertension
- Weight gain



Life-Threatening or Dangerous Side Effects

- Rare neuroleptic malignant syndrome
- Rare seizures

DOSING AND USE

Usual Dosage Range

- Schizophrenia: 400–800 mg/day in 2 doses (oral)
- Predominantly negative symptoms: 50–300 mg/day (oral)
- Intramuscular injection: 600–800 mg/day
- Depression: 150–300 mg/day (oral)

Dosage Forms

- Different formulations may be available in different markets

- Tablet 200 mg, 400 mg, 500 mg
- Intramuscular injection 50 mg/mL, 100 mg/mL

How to Dose

- Initial 400–800 mg/day in 1–2 doses; may need to increase dose to control positive symptoms; maximum generally 2,400 mg/day



Dosing Tips

- ✿ Low doses of sulpiride may be more effective at reducing negative symptoms than positive symptoms in schizophrenia; high doses may be equally effective at reducing both symptom dimensions
- ✿ Lower doses are more likely to be activating; higher doses are more likely to be sedating
- Some patients receive more than 2,400 mg/day
- Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³

Overdose

- Can be fatal; vomiting, agitation, hypotension, hallucinations, CNS depression, sinus tachycardia, arrhythmia, dystonia, dysarthria, hyperreflexia

Long-Term Use

- Apparently safe, but not well studied

Habit Forming

- No

How to Stop

- Recommended to reduce dose over a week
- Slow down-titration (over 6–8 weeks), especially when simultaneously beginning a new antipsychotic while switching (i.e., cross-titration)
- Rapid discontinuation may lead to rebound psychosis and worsening of symptoms
- If antiparkinson agents are being used, they should be continued for a few weeks after sulpiride is discontinued

Pharmacokinetics

- Elimination half-life approximately 6–8 hours
- Excreted largely unchanged



Drug Interactions

- Sulpiride may increase the effects of antihypertensive drugs
- CNS effects may be increased if sulpiride is used with other CNS depressants
- May decrease the effects of levodopa, dopamine agonists
- Antacids or sucralfate may reduce the absorption of sulpiride



Other Warnings/ Precautions

- If signs of neuroleptic malignant syndrome develop, treatment should be immediately discontinued
- Use cautiously in patients with alcohol withdrawal or convulsive disorders because of possible lowering of seizure threshold
- Antiemetic effect of sulpiride may mask signs of other disorders or overdose; suppression of cough reflex may cause asphyxia
- Use with caution in patients with hypertension, cardiovascular disease, pulmonary disease, hyperthyroidism, urinary retention, glaucoma
- May exacerbate symptoms of mania or hypomania
- Use only with caution if at all in Parkinson's disease or Lewy body dementia

Do Not Use

- If patient has pheochromocytoma
- If patient has prolactin-dependent tumor
- If patient is pregnant or nursing
- In children under age 15
- If there is a proven allergy to sulpiride

SPECIAL POPULATIONS

Renal Impairment

- Use with caution; drug may accumulate
- Sulpiride is eliminated by the renal route; in cases of severe renal insufficiency, the dose should be decreased and intermittent treatment or switching to another antipsychotic should be considered

Heptic Impairment

- Use with caution

Cardiac Impairment

- Use with caution

Elderly

- Some patients may tolerate lower doses better
- Although conventional antipsychotics are commonly used for behavioral disturbances in dementia, no agent has been approved for treatment of elderly patients with dementia-related psychosis
- Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death compared to placebo, and also have an increased risk of cerebrovascular events

**Children and Adolescents**

- Not recommended for use in children under age 15
- 14 and older: recommended 3–5 mg/kg per day

**Pregnancy**

- There is a risk of abnormal muscle movements and withdrawal symptoms in newborns whose mothers took an antipsychotic during the third trimester; symptoms may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty feeding
- Potential risks should be weighed against the potential benefits, and sulpiride should be used only if deemed necessary
- Psychotic symptoms may worsen during pregnancy and some form of treatment may be necessary
- Atypical antipsychotics may be preferable to conventional antipsychotics or anticonvulsant mood stabilizers if treatment is required during pregnancy

Breast Feeding

- Some drug is found in mother's breast milk
- Recommended either to discontinue drug or bottle feed
- Immediate postpartum period is a high-risk time for relapse of psychosis

Potential Advantages

- For negative symptoms in some patients

Potential Disadvantages

- Patients who cannot tolerate sedation at high doses
- Patients with severe renal impairment

Primary Target Symptoms

- Positive symptoms of psychosis
- Negative symptoms of psychosis
- Cognitive functioning
- Depressive symptoms
- Aggressive symptoms

**Pearls**

- There is some controversy over whether sulpiride is more effective than older conventionals at treating negative symptoms
- Sulpiride has been used to treat migraine associated with hormonal changes
- Some patients with inadequate response to clozapine may benefit from augmentation with sulpiride
- Sulpiride is poorly absorbed from the gastrointestinal tract and penetrates the blood-brain barrier poorly, which can lead to highly variable clinical responses, especially at lower doses
- Small studies and clinical anecdotes suggest efficacy in depression and anxiety disorders ("neuroses") at low doses
- Patients have very similar antipsychotic responses to any conventional antipsychotic, which is different from atypical antipsychotics where antipsychotic responses of individual patients can occasionally vary greatly from one atypical antipsychotic to another
- Patients with inadequate responses to atypical antipsychotics may benefit from a trial of augmentation with a conventional antipsychotic such as sulpiride or from switching to a conventional antipsychotic such as sulpiride
- However, long-term polypharmacy with a combination of a conventional antipsychotic with an atypical antipsychotic may combine their side effects without clearly augmenting the efficacy of either

- For treatment-resistant patients, especially those with impulsivity, aggression, violence, and self-harm, long-term polypharmacy with 2 atypical antipsychotics or with 1 atypical antipsychotic and 1 conventional antipsychotic may be useful or even necessary while closely monitoring
- In such cases, it may be beneficial to combine 1 depot antipsychotic with 1 oral antipsychotic
- Although a frequent practice by some prescribers, adding 2 conventional antipsychotics together has little rationale and may reduce tolerability without clearly enhancing efficacy



Suggested Reading

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THERAPEUTICS

- Brands**
- Coaxil
 - Stablon
 - Tatinol

see index for additional brand names

- Generic?** Yes



Class

- Neuroscience-based Nomenclature: glutamate; yet to be determined (Glu)
- Glutamatergic modulator
- Often classified as a tricyclic antidepressant, but pharmacologically distinct

Commonly Prescribed for

(bold for FDA approved)

- Major depressive disorder
- Dysthymia
- Anxiety associated with depression



How the Drug Works

- ✳ Modulates glutamatergic neurotransmission, perhaps through potentiation of AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor function

How Long Until It Works

- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Continue treatment until all symptoms are gone (remission)
- Once symptoms gone, continue treating for 1 year for the first episode of depression

- For second and subsequent episodes of depression, treatment may need to be indefinite

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent, or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)



Best Augmenting Combos for Partial Response or Treatment Resistance

- Augmentation has not been systematically studied with tianeptine

Tests

- None recommended for healthy individuals

SIDE EFFECTS

How Drug Causes Side Effects

- ✳ Mild anticholinergic activity (less than some TCAs) could possibly lead to sedative effects, dry mouth, constipation, and blurred vision
- Most side effects are immediate but often go away with time
- ✳ Pharmacologic studies do not indicate tianeptine to be a potent alpha 1 antagonist or H1 antihistamine

Notable Side Effects

- Headache, dizziness, insomnia, sedation
- Nausea, constipation, abdominal pain, dry mouth
- Abnormal dreams
- Increased transaminases
- Tachycardia



Life-Threatening or Dangerous Side Effects

- Theoretically, rare induction of mania and activation of suicidal ideation or behavior
- Cases of activation of suicidal ideation and behavior (suicidality) (short-term did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)
- Hepatitis that can, in exceptional cases, be severe
- Dermatitis bullosus in exceptional cases

Weight Gain



- Not well studied

Sedation



- Occurs in significant minority

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- In a few weeks, switch or add other drugs
- For skin reactions, stop treatment

Best Augmenting Agents for Side Effects

- Augmentation for side effects of tianeptine has not been systematically studied

DOSING AND USE

Usual Dosage Range

- 37.5 mg/day

Dosage Forms

- Tablet 12.5 mg

How to Dose

- 12.5 mg 3 times/day



Dosing Tips

- Tianeptine's rapid elimination necessitates strict adherence to the dosing schedule
- Short half-life means multiple daily doses

Overdose

- Effects are generally mild and nonfatal; unlikely to cause cardiovascular effects

Long-Term Use

- Safe

Habit Forming

- Abuse and dependence may occur, in particular in patients under 50 years of age with a history of drug or alcohol dependence

How to Stop

- Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation
- If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly

Pharmacokinetics

- Not primarily metabolized by CYP 450 enzyme system
- Tianeptine is rapidly eliminated
- Half-life approximately 2.5 hours



Drug Interactions

- Activation and agitation, especially following switching or adding antidepressants, may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of tianeptine
- Other drug interactions not well studied



Other Warnings/ Precautions

- For elective surgery, tianeptine should be stopped 24–48 hours before general anesthesia is administered
- Generally, use only with extreme caution with MAOIs; do not use until 14 days after MAOIs are stopped; do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing tianeptine

- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents
- Warn doctors to pay attention to patients with history of drug dependencies

Do Not Use

- If patient is taking an MAOI
- If patient is pregnant or nursing
- If there is a proven allergy to tianeptine

SPECIAL POPULATIONS

Renal Impairment

- Dose should be reduced for severe impairment to 25 mg/day

Hepatic Impairment

- In patients with severe cirrhosis (class C, Child Plugh's Scale), the dosage should be restricted to 25 mg/day

Cardiac Impairment

- Baseline ECG is recommended

Elderly

- Baseline ECG is recommended for patients over age 50
- Dose should be reduced to 25 mg/day
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Tianeptine is not recommended for use in children or adolescents under 18
- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients



Pregnancy

- Not recommended for use during pregnancy

Breast Feeding

- Some drug is found in mother's breast milk
- Not recommended for use during pregnancy
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients, this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Elderly patients

Potential Disadvantages

- Patients who have difficulty being compliant with multiple daily dosing

Primary Target Symptoms

- Depressed mood
- Symptoms of anxiety



Pearls

- Possibly a unique mechanism of action as a glutamatergic antidepressant
- It is not metabolized by CYP450; therefore, the risk of pharmacokinetic drug-drug interactions is minimized



Suggested Reading

Kasper S, McEwen BS. Neurobiological and clinical effects of the antidepressant tianeptine. *CNS Drugs* 2008;22(1):15–26.

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(Stablon): from monoamine hypothesis to glutamatergic modulation. *Mol Psychiatry* 2010;15:237–49.

Svenningsson P, Bateup H, Qi H, et al. Involvement of AMPA receptor phosphorylation in antidepressant actions with special reference to tianeptine. *Eur J Neuosci* 2007;26:3509–17.

Wagstaff AJ, Ormrod D, Spencer CM. Tianeptine: a review of its use in depressive disorders. *CNS Drugs* 2001;15(3):231–59.

THERAPEUTICS

Brands • Parnate
see index for additional brand names

Generic? Yes

**Class**

- Neuroscience-based Nomenclature: serotonin, norepinephrine, dopamine multimodal enzyme inhibitor (SN-MM)
- Monoamine oxidase inhibitor (MAOI)

Commonly Prescribed for

(bold for FDA approved)

- Major depressive episode without melancholia
- Treatment-resistant depression
- Treatment-resistant panic disorder
- Treatment-resistant social anxiety disorder

**How the Drug Works**

- Irreversibly blocks monoamine oxidase (MAO) from breaking down norepinephrine, serotonin, and dopamine
- This presumably boosts noradrenergic, serotonergic, and dopaminergic neurotransmission
- ★ As the drug is structurally related to amphetamine, it may have some stimulant-like actions due to monoamine release and reuptake inhibition

How Long Until It Works

- Some patients may experience stimulant-like actions early in dosing
- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Continue treatment until all symptoms are gone (remission)

- Once symptoms gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders may also need to be indefinite

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some patients who have an initial response may relapse even though they continue treatment, sometimes called "poop-out"
- Consider increasing dose, switching to another agent, or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer

**Best Augmenting Combos for Partial Response or Treatment Resistance**

- ★ Augmentation of MAOIs has not been systematically studied, and this is something for the expert, to be done with caution and with careful monitoring
- ★ A stimulant such as d-amphetamine or methylphenidate (with caution; may activate bipolar disorder and suicidal ideation; may elevate blood pressure)
- Lithium
- Mood-stabilizing anticonvulsants
- Atypical antipsychotics (with special caution for those agents with monoamine reuptake blocking properties, such as ziprasidone and zotepine)

Tests

- Patients should be monitored for changes in blood pressure
- Patients receiving high doses or long-term treatment should have hepatic function evaluated periodically

SIDE EFFECTS

How Drug Causes Side Effects

- Theoretically due to increases in monoamines in parts of the brain and body and at receptors other than those that cause therapeutic actions (e.g., unwanted actions of serotonin in sleep centers causing insomnia, unwanted actions of norepinephrine on vascular smooth muscle causing hypertension, etc.)
- Side effects are generally immediate, but immediate side effects often disappear in time

Notable Side Effects

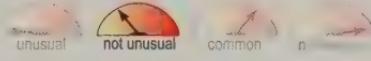
- Agitation, anxiety, insomnia, weakness, sedation, dizziness
- Constipation, dry mouth, nausea, diarrhea, change in appetite, weight gain
- Sexual dysfunction
- Orthostatic hypotension (dose-related); syncope may develop at high doses



Life-Threatening or Dangerous Side Effects

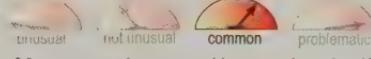
- Hypertensive crisis (especially when MAOIs are used with certain tyramine-containing foods or prohibited drugs)
- Induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)
- Seizures
- Hepatotoxicity

Weight Gain



- Occurs in significant minority

Sedation



- Many experience and/or can be significant in amount
- Can also cause activation

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose

- Take at night if daytime sedation; take in daytime if overstimulated at night
- Switch after appropriate washout to an SSRI or newer antidepressant

Best Augmenting Agents for Side Effects

- Trazodone (with caution) for insomnia
- Benzodiazepines for insomnia
- * Single oral or sublingual dose of a calcium channel blocker (e.g., nifedipine) for urgent treatment of hypertension due to drug interaction or dietary tyramine
- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 30 mg/day in divided doses

Dosage Forms

- Tablet 10 mg

How to Dose

- Initial 30 mg/day in divided doses; after 2 weeks increase by 10 mg/day each 1–3 weeks; maximum 60 mg/day



Dosing Tips

- Orthostatic hypotension, especially at high doses, may require splitting into 3–4 daily doses
- Patients receiving high doses may need to be evaluated periodically for effects on the liver

Overdose

- Dizziness, sedation, ataxia, headache, insomnia, restlessness, anxiety, irritability; cardiovascular effects, confusion, respiratory depression, or coma may also occur

Long-Term Use

- May require periodic evaluation of hepatic function
- MAOIs may lose efficacy long-term

Habit Forming

- Some patients have developed dependence to MAOIs

How to Stop

- Generally no need to taper, as the drug wears off slowly over 2–3 weeks

Pharmacokinetics

- Clinical duration of action may be up to 14 days due to irreversible enzyme inhibition



Drug Interactions

- Tramadol may increase the risk of seizures in patients taking an MAOI
- Can cause a fatal “serotonin syndrome” when combined with drugs that block serotonin reuptake, so do not use with a serotonin reuptake inhibitor or for 5 half-lives after stopping the serotonin reuptake inhibitor (see Table 1 after Pearls)
- Hypertensive crisis with headache, intracranial bleeding, and death may result from combining MAOIs with sympathomimetic drugs (e.g., amphetamines, methylphenidate, cocaine, dopamine, epinephrine, norepinephrine, and related compounds methyldopa, levodopa, L-tryptophan, L-tyrosine, and phenylalanine)
- Do not combine with another MAOI, alcohol, or guanethidine
- Adverse drug reactions can result from combining MAOIs with tricyclic/tetracyclic antidepressants and related compounds, including carbamazepine, cyclobenzaprine, and mirtazapine, and should be avoided except by experts to treat difficult cases
- MAOIs in combination with spinal anesthesia may cause combined hypotensive effects
- Combination of MAOIs and CNS depressants may enhance sedation and hypotension



Other Warnings/ Precautions

- Use requires low tyramine diet (see Table 2 after Pearls)
- Patient and prescriber must be vigilant to potential interactions with any drug, including antihypertensives and over-the-counter cough/cold preparations
- Over-the-counter medications to avoid include cough and cold preparations, including those containing

dextromethorphan, nasal decongestants (tablets, drops, or spray), hay-fever medications, sinus medications, asthma inhalant medications, anti-appetite medications, weight reducing preparations, “pep” pills (see Table 3 after Pearls)

- Hypoglycemia may occur in diabetic patients receiving insulin or oral antidiabetic agents
- Use cautiously in patients receiving reserpine, anesthetics, disulfiram, metrizamide, anticholinergic agents
- Tranylcypromine is not recommended for use in patients who cannot be monitored closely
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is taking meperidine (pethidine)
- If patient is taking a sympathomimetic agent or taking guanethidine
- If patient is taking another MAOI
- If patient is taking any agent that can inhibit serotonin reuptake (e.g., SSRIs, sibutramine, tramadol, milnacipran, duloxetine, venlafaxine, clomipramine, etc.)
- If patient is taking diuretics, dextromethorphan
- If patient has pheochromocytoma
- If patient has cardiovascular or cerebrovascular disease
- If patient has frequent or severe headaches
- If patient is undergoing elective surgery and requires general anesthesia
- If patient has a history of liver disease or abnormal liver function tests
- If patient is taking a prohibited drug
- If patient is not compliant with a low-tyramine diet
- If there is a proven allergy to tranylcypromine

SPECIAL POPULATIONS

Renal Impairment

- Use with caution – drug may accumulate in plasma
- May require lower than usual adult dose

Hepatic Impairment

- Tranylcypromine should not be used in patients with history of hepatic impairment or in patients with abnormal liver function tests

Cardiac Impairment

- Contraindicated in patients with any cardiac impairment

Elderly

- Initial dose lower than usual adult dose
- Elderly patients may have greater sensitivity to adverse effects
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Not generally recommended for use in children under age 18
- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLL) or final rule) applies only to prescription drugs and will be

phased in gradually for drugs approved on or after June 30, 2001

- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester
- Should evaluate patient for treatment with an antidepressant with a better risk/benefit ratio

Breast Feeding

- Some drug is found in mother's breast milk
- Effects on infant unknown
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Should evaluate patient for treatment with an antidepressant with a better risk/benefit ratio

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Atypical depression
- Severe depression
- Treatment-resistant depression or anxiety disorders

Potential Disadvantages

- Requires compliance to dietary restrictions, concomitant drug restrictions
- Patients with cardiac problems or hypertension
- Multiple daily doses

Primary Target Symptoms

- Depressed mood
- Somatic symptoms
- Sleep and eating disturbances
- Psychomotor retardation
- Morbid preoccupation



Pearls

- MAOIs are generally reserved for second-line use after SSRIs, SNRIs, and combinations of newer antidepressants have failed

- Patient should be advised not to take any prescription or over-the-counter drugs without consulting their doctor because of possible drug interactions with the MAOI
- Headache is often the first symptom of hypertensive crisis
- The rigid dietary restrictions may reduce compliance (see Table 2 after Pearls)
- Mood disorders can be associated with eating disorders (especially in adolescent females), and tranylcypromine can be used to treat both depression and bulimia
- MAOIs are a viable second-line treatment option in depression, but are not frequently used

- * Myths about the danger of dietary tyramine can be exaggerated, but prohibitions against concomitant drugs often not followed closely enough**
- Orthostatic hypotension, insomnia, and sexual dysfunction are often the most troublesome common side effects
 - * MAOIs should be for the expert, especially if combining with agents of potential risk (e.g., stimulants, trazodone, TCAs)**
 - * MAOIs should not be neglected as therapeutic agents for the treatment-resistant**

- Although generally prohibited, a heroic but potentially dangerous treatment for severely treatment-resistant patients is for an expert to give a tricyclic/tetracyclic antidepressant other than clomipramine simultaneously with an MAOI for patients who fail to respond to numerous other antidepressants
- Use of MAOIs with clomipramine is always prohibited because of the risk of serotonin syndrome and death
- Amoxapine may be the preferred tricyclic/tetracyclic antidepressant to combine with an MAOI in heroic cases due to its theoretically protective 5HT2A antagonist properties
- If this option is elected, start the MAOI with the tricyclic/tetracyclic antidepressant simultaneously at low doses after appropriate drug washout, then alternately increase doses of these agents every few days to a week as tolerated
- Although very strict dietary and concomitant drug restrictions must be observed to prevent hypertensive crises and serotonin syndrome, the most common side effects of MAOI and tricyclic/tetracyclic combinations may be weight gain and orthostatic hypotension

Table 1. Drugs contraindicated due to risk of serotonin syndrome/toxicity

Do Not Use:			
Antidepressants	Drugs of Abuse	Opioids	Other
SSRIs	MDMA (ecstasy)	Meperidine	Non-subcutaneous sumatriptan
SNRIs	Cocaine	Tramadol	Chlorpheniramine
Clomipramine	Methamphetamine	Methadone	Brompheniramine
St. John's wort	High-dose or injected amphetamine	Fentanyl	Dextromethorphan
			Procarbazine?

TRANYLCYPROMINE (continued)

Table 2. Dietary guidelines for patients taking MAOIs

Foods to avoid*	Foods allowed
Dried, aged, smoked, fermented, spoiled, or improperly stored meat, poultry, and fish	Fresh or processed meat, poultry, and fish; properly stored pickled or smoked fish
Broad bean pods	All other vegetables
Aged cheeses	Processed cheese slices, cottage cheese, ricotta cheese, yogurt, cream cheese
Tap and unpasteurized beer	Canned or bottled beer and alcohol
Marmite	Brewer's and baker's yeast
Sauerkraut, kimchee	
Soy products/tofu	Peanuts
Banana peel	Bananas, avocados, raspberries
Tyramine-containing nutritional supplement	

*Not necessary for 6-mg transdermal or low-dose oral selegiline

Table 3. Drugs that boost norepinephrine: should only be used with caution with MAOIs

Use With Caution:			
Decongestants	Stimulants	Antidepressants with norepinephrine reuptake inhibition	Other
Phenylephrine	Amphetamines	Most tricyclics	Phentermine
Pseudoephedrine	Methylphenidate	NRIs	Local anesthetics containing vasoconstrictors
	Cocaine	NDRIs	
	Methamphetamine		
	Modafinil		Tapentadol
	Armodafinil		



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THERAPEUTICS

- Brands**
 - Desyrel
 - Oleptro

see index for additional brand names

- Generic?** Yes



Class

- Neuroscience-based Nomenclature: serotonin receptor antagonist (S-MM)
- SARI (serotonin 2 antagonist/reuptake inhibitor); antidepressant; hypnotic

Commonly Prescribed for

(bold for FDA approved)

- Depression**
- Insomnia (primary and secondary)
- Anxiety



How the Drug Works

- Blocks serotonin 2A receptors potently
- Blocks serotonin reuptake pump (serotonin transporter) less potently

How Long Until It Works

- * Onset of therapeutic actions in insomnia are immediate if dosing is correct
- Onset of therapeutic actions in depression usually not immediate, but often delayed 2–4 weeks whether given as an adjunct to another antidepressant or as a monotherapy
- If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms in depression and to reduce symptoms of chronic insomnia

If It Works

- * For insomnia, use possibly can be indefinite as there is no reliable evidence of tolerance, dependence, or withdrawal, but few long-term studies
- For secondary insomnia, if underlying condition (e.g., depression, anxiety disorder) is in remission, trazodone treatment may be discontinued if insomnia does not reemerge
- The goal of treatment for depression is complete remission of current symptoms of depression as well as prevention of future relapses

- Treatment most often reduces or even eliminates symptoms of depression, but is not a cure since symptoms can recur after medicine stopped
- Continue treatment until all symptoms of depression are gone (remission)
- Once symptoms of depression are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite

If It Doesn't Work

- For insomnia, try escalating doses or switch to another agent
- Many patients have only a partial antidepressant response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent for treatment of depression
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer



Best Augmenting Combos for Partial Response or Treatment Resistance

- Trazodone is not frequently used as a monotherapy for insomnia, but can be combined with sedative hypnotic benzodiazepines in difficult cases
- Trazodone is most frequently used in depression as an augmenting agent to numerous psychotropic drugs
- Trazodone can not only improve insomnia in depressed patients treated with antidepressants, but can also be an effective booster of antidepressant actions of other antidepressants (use combinations of antidepressants with caution as this

TRAZODONE (continued)

may activate bipolar disorder and suicidal ideation)

- Trazodone can also improve insomnia in numerous other psychiatric conditions (e.g., bipolar disorder, schizophrenia, alcohol withdrawal) and be added to numerous other psychotropic drugs (e.g., lithium, mood stabilizers, antipsychotics)

Tests

- None for healthy individuals

SIDE EFFECTS

How Drug Causes Side Effects

- Sedative effects may be due to antihistamine properties
- Blockade of alpha adrenergic 1 receptors may explain dizziness, sedation, and hypotension
- Most side effects are immediate but often go away with time

Notable Side Effects

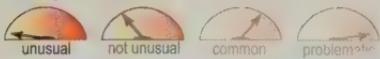
- Nausea, vomiting, edema, blurred vision, constipation, dry mouth
- Dizziness, sedation, fatigue, headache, incoordination, tremor
- Hypotension, syncope
- Occasional sinus bradycardia (long-term)
- Rare rash



Life-Threatening or Dangerous Side Effects

- Rare priapism
- Rare seizures
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Reported but not expected

Sedation



- Many experience and/or can be significant in amount

What to Do About Side Effects

- Wait
- Wait
- Wait
- Take larger dose at night to prevent daytime sedation
- Switch to another agent

Best Augmenting Agents for Side Effects

- Most side effects cannot be improved with an augmenting agent
- Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of trazodone

DOSING AND USE

Usual Dosage Range

- 150–600 mg/day
- 150–375 mg/day (extended-release)

Dosage Forms

- Tablet 50 mg scored, 100 mg scored, 150 mg, 150 mg with povidone scored, 300 mg with povidone scored
- Extended-release tablet 150 mg scored, 300 mg scored

How to Dose

- Depression as a monotherapy: initial 150 mg/day in divided doses; can increase every 3–4 days by 50 mg/day as needed; maximum 400 mg/day (outpatient) or 600 mg/day (inpatient), split into 2 daily doses
- Insomnia: initial 25–50 mg at bedtime; increase as tolerated, usually to 50–100 mg/day, but some patients may require up to full antidepressant dose range
- Augmentation of other antidepressants in the treatment of depression: dose as recommended for insomnia
- Extended-release: initial 150 mg once daily; may be increased by 75 mg/day every 3 days; maximum dose generally 375 mg/day



Dosing Tips

- Start low and go slow

- ✿ Patients can have carryover sedation, ataxia, and intoxicated-like feeling if dosed too aggressively, particularly when initiating dosing
- ✿ Do not discontinue trials if ineffective at low doses (<50 mg) as many patients with difficult cases may respond to higher doses (150–300 mg, even up to 600 mg in some cases)
- For relief of daytime anxiety, can give part of the dose in the daytime if not too sedating
- Although use as a monotherapy for depression is usually in divided doses due to its short half-life, use as an adjunct is often effective and best tolerated once daily at bedtime

Overdose

- Rarely lethal; sedation, vomiting, priapism, respiratory arrest, seizure, EKG changes

Long-Term Use

- Safe

Habit Forming

- No

How to Stop

- Taper is prudent to avoid withdrawal effects, but tolerance, dependence, and withdrawal effects have not been reliably demonstrated

Pharmacokinetics

- Metabolized by CYP450 3A4
- Half-life is biphasic; first phase is approximately 3–6 hours; second phase is approximately 5–9 hours



Drug Interactions

- Tramadol increases the risk of seizures in patients taking an antidepressant
- Fluoxetine and other SSRIs may raise trazodone plasma levels
- Trazodone may block the hypotensive effects of some antihypertensive drugs
- Trazodone may increase digoxin or phenytoin concentrations
- Trazodone may interfere with the antihypertensive effects of clonidine
- Generally, do not use with MAOIs, including 14 days after MAOIs are stopped

- Reports of increased and decreased prothrombin time in patients taking warfarin and trazodone



Other Warnings/ Precautions

- Possibility of additive effects if trazodone is used with other CNS depressants
- Treatment should be discontinued if prolonged penile erection occurs because of the risk of permanent erectile dysfunction
- Advise patients to seek medical attention immediately if painful erections occur lasting more than 1 hour
- Generally, priapism reverses spontaneously, while penile blood flow and other signs being monitored, but in urgent cases, local phenylephrine injections or even surgery may be indicated
- Use with caution in patients with history of seizures
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is taking an MAOI, but see Pearls
- If there is a proven allergy to trazodone

SPECIAL POPULATIONS

Renal Impairment

- No dose adjustment necessary

Hepatic Impairment

- Drug should be used with caution

Cardiac Impairment

- Trazodone may be arrhythmogenic
- Monitor patients closely
- Not recommended for use during recovery from myocardial infarction

Elderly

- Elderly patients may be more sensitive to adverse effects and may require lower doses
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Safety and efficacy have not been established, but trazodone has been used for behavioral disturbances, depression, and night terrors
- Children require lower initial dose and slow titration
- Boys may be even more sensitive to having prolonged erections than adult men



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Avoid use during first trimester

- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy

Breast Feeding

- Some drug is found in mother's breast milk
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients, this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- For insomnia when it is preferred to avoid the use of dependence-forming agents
- As an adjunct to the treatment of residual anxiety and insomnia with other antidepressants
- Depressed patients with anxiety
- Patients concerned about sexual side effects or weight gain

Potential Disadvantages

- For patients with fatigue, hypersomnia
- For patients intolerant to sedating effects

Primary Target Symptoms

- Depression
- Anxiety
- Sleep disturbances



Pearls

- May be less likely than some antidepressants to precipitate hypomania or mania

- Preliminary data suggest that trazodone may be effective treatment for drug-induced dyskinesias, perhaps in part because it reduces accompanying anxiety
- Trazodone may have some efficacy in treating agitation and aggression associated with dementia
- May cause sexual dysfunction only infrequently
- Can cause carryover sedation, sometimes severe, if dosed too high
- Often not tolerated as a monotherapy for moderate to severe cases of depression, as many patients cannot tolerate high doses (>150 mg)
- Do not forget to try at high doses, up to 600 mg/day, if lower doses well tolerated but ineffective

- ✿ For the expert psychopharmacologist, trazodone can be used cautiously for insomnia associated with MAOIs, despite the warning – must be attempted only if patients closely monitored and by experts experienced in the use of MAOIs
- Priapism may occur in 1 in 8,000 men
 - Early indications of impending priapism may be slow penile detumescence when awakening from REM sleep
 - When using to treat insomnia, remember that insomnia may be a symptom of some other primary disorder, and not a primary disorder itself, and thus warrant evaluation for comorbid psychiatric and/or medical conditions
 - Rarely, patients may complain of visual “trails” or after-images on trazodone



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THERAPEUTICS

Brands • Cytomel

see index for additional brand names

Generic? Yes

Class

- Synthetic hormone; antidepressant adjunct

Commonly Prescribed for

(bold for FDA approved)

- Replacement or supplemental therapy in patients with hypothyroidism (except transient hypothyroidism during the recovery phase of subacute thyroiditis)
- Pituitary thyroid-stimulating hormone (TSH) suppressant in the treatment or prevention of various types of euthyroid goiters
- Major depressive disorder (adjunct)



How the Drug Works

- Hypothetically boosts monoamine actions in the CNS
- May work synergistically with traditional antidepressants

How Long Until It Works (for depression)

- Can work within days, but therapeutic effects may be delayed for up to 8 weeks

If It Works (for depression)

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Continue treatment until all symptoms are gone (remission) or significantly reduced
- Once symptoms gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite

If It Doesn't Work (for depression)

- Many patients only have a partial response where some symptoms are improved but

others persist (especially insomnia, fatigue, and problems concentrating)

- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some patients who have an initial response may relapse even though they continue treatment, sometimes called "poop-out"
- Consider switching to another antidepressant or adding a different augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and switch to a mood stabilizer



Best Augmenting Combos for Partial Response or Treatment Resistance

- Triiodothyronine is itself an augmenting agent for partial response in depression

Tests

- Periodic assessment of thyroid status
- Administration of triiodothyronine may lead to mild hyperthyroidism with reduced levels of TSH

SIDE EFFECTS

How Drug Causes Side Effects

- Increases in thyroid hormone concentrations

Notable Side Effects

- Hyperthyroidism (headache, irritability, nervousness, sweating, arrhythmia, increased bowel motility, menstrual irregularities)
- Possible acceleration of bone demineralization, especially in postmenopausal women (controversial)



Life-Threatening or Dangerous Side Effects

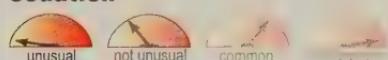
- Angina pectoris, congestive heart failure
- Shock

Weight Gain



- Reported but not expected
- May cause weight loss

Sedation



- Reported but not expected

What to Do About Side Effects

- Wait
- Wait
- Wait
- In a few weeks, switch to another agent

Best Augmenting Agents for Side Effects

- Often best to try another treatment prior to resorting to augmentation strategies to treat side effects

DOSING AND USE

Usual Dosage Range

- 25–50 mcg/day

Dosage Forms

- Tablet 5 mcg, 25 mcg, 50 mcg

How to Dose

- Initial 25 mcg/day; if no response can increase to 50 mcg/day after 2–4 weeks



Dosing Tips

- Monitor TSH levels to determine efficacy or thyroid actions in the periphery and to guide dosing
- If no effects on depressed mood, may want to discontinue in 8–12 weeks
- To assess efficacy in stabilizing mood in combination with other mood stabilizers, may need to monitor for a few months

Overdose

- Chest pain, increased pulse rate, palpitations, excessive sweating, heat intolerance, nervousness

Long-Term Use

- Has not been evaluated in controlled studies, but long-term treatment of major depressive disorder is generally necessary

Habit Forming

- No

How to Stop

- Taper not necessary

Pharmacokinetics

- Half-life approximately 2.5 days



Drug Interactions

- Thyroid hormones appear to increase catabolism of vitamin K-dependent clotting factors; patients stabilized on oral anticoagulants who are treated with triiodothyronine should be watched very closely when triiodothyronine is started and may require dose reduction of the oral anticoagulant
- Initiating thyroid replacement therapy may cause increases in insulin or oral hypoglycemic requirements; patients receiving insulin or oral hypoglycemics should be closely watched during initiation of triiodothyronine
- Cholestyramine binds both T4 and T3 in the intestine, thus impairing absorption of these thyroid hormones; therefore, 4 to 5 hours should elapse between administration of cholestyramine and thyroid hormones
- Use of thyroid products with imipramine and other TCAs may increase receptor sensitivity and enhance antidepressant activity; transient cardiac arrhythmias have been observed; thyroid hormone activity may also be enhanced
- Thyroid preparations may potentiate the toxic effects of digitalis
- Use with caution with ketamine; may cause hypertension and tachycardia
- Use with catecholamines may increase their adrenergic effects; careful observation is required



Other Warnings/ Precautions

- Use of thyroid hormones in the therapy of obesity, alone or in combination, is not

effective at doses within the range of daily hormonal requirements; larger doses may produce serious or even life-threatening manifestations of toxicity, particularly when given in association with sympathomimetic amines

- Use of thyroid hormones is not justified for the treatment of male or female infertility unless accompanied by hypothyroidism
- Use with caution in patients in whom the integrity of the cardiovascular system is suspected, including elderly patients or those with angina pectoris
- Thyroid hormone therapy in patients with concomitant diabetes mellitus or insipidus or adrenal cortical insufficiency aggravates the intensity of their symptoms

Do Not Use

- If patient has uncorrected adrenal cortical insufficiency
- If patient has untreated thyrotoxicosis
- If there is a proven allergy to triiodothyronine

SPECIAL POPULATIONS

Renal Impairment

- No dose adjustment necessary

Hepatic Impairment

- No dose adjustment necessary

Cardiac Impairment

- Use with caution
- Requires dose reduction: initial 5 mcg; increase by no more than 5 mcg at 2-week intervals; reduce dose if cardiovascular disease is aggravated

Elderly

- Some patients may tolerate lower doses better



Children and Adolescents

- Thyroid hormone is used safely in infants, children, and adolescents for hypothyroidism
- Not studied for use as adjunct in depression



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus
- Thyroid hormones do not readily cross the placental barrier, and the clinical experience to date does not indicate any adverse effect on fetuses when thyroid hormones are administered to pregnant women

Breast Feeding

- Some drug is found in mother's breast milk
- No known adverse effects but use should be cautious
- Must weigh benefits of breast feeding with risks and benefits of treatment versus nontreatment to both the infant and the mother
- For many patients, this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients with lethargy and fatigue
- Patients with unstable or rapidly fluctuating mood

Potential Disadvantages

- Patients with osteoporosis
- Patients already taking thyroid replacement

Primary Target Symptoms

- Depressed mood



Pearls

- Have periodic monitoring by primary care physician, including neck examination and thyroid palpation

TRIIODOTHYRONINE (continued)

- Generally well tolerated, especially compared to other augmentation options for depression
- May be useful in stabilizing fluctuating mood states as well as improving depressed mood



Suggested Reading

Aronson R, Offman HJ, Joffe RT, et al. Triiodothyronine augmentation in the treatment of refractory depression: a meta-analysis. *Arch Gen Psychiatry* 1996;53:842–8.

Connolly KR, Thase ME. If at first you don't succeed: a review of the evidence for antidepressant augmentation, combination and switching strategies. *Drugs* 2011;71(1):43–64.

Garlow SJ, Dunlop BW, Ninan PT, Nemeroff CB. The combination of triiodothyronine (T3) and sertraline is not superior to sertraline monotherapy in the treatment of

major depressive disorder. *J Psychiatr Res* 2012;46(11):1406–13.

Hage MP, Azar ST. The link between thyroid function and depression. *J Thyroid Res* 2012;2012:590648.

Nierenberg AA, Fava M, Trivedi MH, et al. A comparison of lithium and T(3) augmentation following two failed medication treatments for depression: a STAR*D report. *Am J Psychiatry* 2006;163:1519–30.

THERAPEUTICS

Brands • Surmontil
see index for additional brand names

Generic? Yes

**Class**

- Neuroscience-based Nomenclature: dopamine and serotonin receptor antagonist (DS-RAn)
- Tricyclic antidepressant (TCA)
- Serotonin and norepinephrine/noradrenaline reuptake inhibitor

Commonly Prescribed for

(bold for FDA approved)

- **Depression**
- **Endogenous depression**
- Anxiety
- Insomnia
- Neuropathic pain/chronic pain
- Treatment-resistant depression

**How the Drug Works**

- Boosts neurotransmitters serotonin and norepinephrine/noradrenaline
- Blocks serotonin reuptake pump (serotonin transporter), presumably increasing serotonergic neurotransmission
- Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing noradrenergic neurotransmission
- Presumably desensitizes both serotonin 1A receptors and beta adrenergic receptors
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, trimipramine can increase dopamine transmission in this part of the brain

How Long Until It Works

- May have immediate effects in treating insomnia, agitation, or anxiety
- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all

- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment of depression is complete remission of current symptoms as well as prevention of future relapses
- The goal of treatment of chronic neuropathic pain is to reduce symptoms as much as possible, especially in combination with other treatments
- Treatment of depression most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Treatment of chronic neuropathic pain may reduce symptoms, but rarely eliminates them completely, and is not a cure since symptoms can recur after medicine is stopped
- Continue treatment of depression until all symptoms are gone (remission)
- Once symptoms of depression are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders and chronic pain may also need to be indefinite, but long-term treatment is not well studied in these conditions

If It Doesn't Work

- Many depressed patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other depressed patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer



Best Augmenting Combos for Partial Response or Treatment Resistance

- Lithium, buspirone, thyroid hormone (for depression)
- Gabapentin, tiagabine, other anticonvulsants, even opiates if done by experts while monitoring carefully in difficult cases (for chronic pain)

Tests

- Baseline ECG is recommended for patients over age 50
- Since tricyclic and tetracyclic antidepressants are frequently associated with weight gain, before starting treatment, weigh all patients and determine if the patient is already overweight (BMI 25.0–29.9) or obese (BMI ≥ 30)
- Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–125 mg/dL), diabetes (fasting plasma glucose > 126 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management
- Monitor weight and BMI during treatment
- While giving a drug to a patient who has gained $>5\%$ of initial weight, consider evaluating for the presence of pre-diabetes, diabetes, or dyslipidemia, or consider switching to a different antipsychotic
- EKGs may be useful for selected patients (e.g., those with personal or family history of QTc prolongation; cardiac arrhythmia; recent myocardial infarction; uncompensated heart failure; or taking agents that prolong QTc interval such as pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin, etc.)
- Patients at risk for electrolyte disturbances (e.g., patients on diuretic therapy) should have baseline and periodic serum potassium and magnesium measurements

SIDE EFFECTS

How Drug Causes Side Effects

- Anticholinergic activity may explain sedative effects, dry mouth, constipation, and blurred vision
- Sedative effects and weight gain may be due to antihistamine properties
- Blockade of alpha adrenergic 1 receptors may explain dizziness, sedation, and hypotension
- Cardiac arrhythmias and seizures, especially in overdose, may be caused by blockade of ion channels

Notable Side Effects

- Blurred vision, constipation, urinary retention, increased appetite, dry mouth, nausea, diarrhea, heartburn, unusual taste in mouth, weight gain
- Fatigue, weakness, dizziness, sedation, headache, anxiety, nervousness, restlessness
- Sexual dysfunction (impotence, change in libido)
- Sweating, rash, itching



Life-Threatening or Dangerous Side Effects

- Paralytic ileus, hyperthermia (TCAs + anticholinergic agents)
- Lowered seizure threshold and rare seizures
- Orthostatic hypotension, sudden death, arrhythmias, tachycardia
- QTc prolongation
- Hepatic failure, extrapyramidal symptoms
- Increased intraocular pressure
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Many experience and/or can be significant in amount
- Can increase appetite and carbohydrate craving

Sedation



- Many experience and/or can be significant in amount
- Tolerance to sedative effects may develop with long-term use

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- Switch to an SSRI or newer antidepressant

Best Augmenting Agents for Side Effects

- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- 50–150 mg/day

Dosage Forms

- Capsule 25 mg, 50 mg, 100 mg

How to Dose

- Initial 25 mg/day at bedtime; increase by 75 mg every 3–7 days
- 75 mg/day in divided doses; increase to 150 mg/day; maximum 200 mg/day; hospitalized patients may receive doses up to 300 mg/day



Dosing Tips

- If given in a single dose, should generally be administered at bedtime because of its sedative properties
- If given in split doses, largest dose should generally be given at bedtime because of its sedative properties
- If patients experience nightmares, split dose and do not give large dose at bedtime
- Patients treated for chronic pain may only require lower doses
- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar

disorder, and switch to a mood stabilizer or an atypical antipsychotic

Overdose

- Death may occur; CNS depression, convulsions, cardiac dysrhythmias, severe hypotension, EKG changes, coma

Long-Term Use

- Safe

Habit Forming

- No

How to Stop

- Taper to avoid withdrawal effects
- Even with gradual dose reduction some withdrawal symptoms may appear within the first 2 weeks
- Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation
- If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly

Pharmacokinetics

- Substrate for CYP450 2D6, 2C19, and 2C9
- Half-life approximately 7–23 hours



Drug Interactions

- Tramadol increases the risk of seizures in patients taking TCAs
- Use of TCAs with anticholinergic drugs may result in paralytic ileus or hyperthermia
- Fluoxetine, paroxetine, bupropion, duloxetine, and other CYP450 2D6 inhibitors may increase TCA concentrations
- Cimetidine may increase plasma concentrations of TCAs and cause anticholinergic symptoms
- Phenothiazines or haloperidol may raise TCA blood concentrations
- May alter effects of antihypertensive drugs; may inhibit hypotensive effects of clonidine
- Use with sympathomimetic agents may increase sympathetic activity
- Methylphenidate may inhibit metabolism of TCAs
- Activation and agitation, especially following switching or adding antidepressants, may represent the

induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of trimipramine



Other Warnings/ Precautions

- Add or initiate other antidepressants with caution for up to 2 weeks after discontinuing trimipramine
- Generally, do not use with MAOIs, including 14 days after MAOIs are stopped; do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing trimipramine, but see Pearls
- Use with caution in patients with history of seizures, urinary retention, angle-closure glaucoma, hyperthyroidism
- TCAs can increase QTc interval, especially at toxic doses, which can be attained not only by overdose but also by combining with drugs that inhibit TCA metabolism via CYP450 2D6, potentially causing torsade de pointes-type arrhythmia or sudden death
- Because TCAs can prolong QTc interval, use with caution in patients who have bradycardia or who are taking drugs that can induce bradycardia (e.g., beta blockers, calcium channel blockers, clonidine, digitalis)
- Because TCAs can prolong QTc interval, use with caution in patients who have hypokalemia and/or hypomagnesemia or who are taking drugs that can induce hypokalemia and/or magnesemia (e.g., diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactide)
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately

- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is recovering from myocardial infarction
- If patient is taking agents capable of significantly prolonging QTc interval (e.g., pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin)
- If there is a history of QTc prolongation or cardiac arrhythmia, recent acute myocardial infarction, uncompensated heart failure
- If patient is taking drugs that inhibit TCA metabolism, including CYP450 2D6 inhibitors, except by an expert
- If there is reduced CYP450 2D6 function, such as patients who are poor 2D6 metabolizers, except by an expert and at low doses
- If there is a proven allergy to trimipramine

SPECIAL POPULATIONS

Renal Impairment

- Use with caution; may need to lower dose

Hepatic Impairment

- Use with caution; may need to lower dose

Cardiac Impairment

- Baseline ECG is recommended
- TCAs have been reported to cause arrhythmias, prolongation of conduction time, orthostatic hypotension, sinus tachycardia, and heart failure, especially in the diseased heart
- Myocardial infarction and stroke have been reported with TCAs
- TCAs produce QTc prolongation, which may be enhanced by the existence of bradycardia, hypokalemia, congenital or acquired long QTc interval, which should be evaluated prior to administering trimipramine
- Use with caution if treating concomitantly with a medication likely to produce prolonged bradycardia, hypokalemia, slowing of intracardiac conduction, or prolongation of the QTc interval
- Avoid TCAs in patients with a known history of QTc prolongation, recent acute

myocardial infarction, and uncompensated heart failure

- TCAs may cause a sustained increase in heart rate in patients with ischemic heart disease and may worsen (decrease) heart rate variability, an independent risk of mortality in cardiac populations
- Since SSRIs may improve (increase) heart rate variability in patients following a myocardial infarct and may improve survival as well as mood in patients with acute angina or following a myocardial infarction, these are more appropriate agents for cardiac population than tricyclic/tetracyclic antidepressants

✳ Risk/benefit ratio may not justify use of TCAs in cardiac impairment

Elderly

- Baseline ECG is recommended for patients over age 50
- May be more sensitive to anticholinergic, cardiovascular, hypotensive, and sedative effects
- Initial dose 50 mg/day; increase gradually up to 100 mg/day
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Not recommended for use in children under age 12
- Several studies show lack of efficacy of TCAs for depression
- May be used to treat enuresis or hyperactive/impulsive behaviors
- Some cases of sudden death have occurred in children taking TCAs

- Adolescents: initial dose 50 mg/day; increase gradually up to 100 mg/day



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Crosses the placenta
- Adverse effects have been reported in infants whose mothers took a TCA (lethargy, withdrawal symptoms, fetal malformations)
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy

Breast Feeding

- Some drug is found in mother's breast milk
- ✳ Recommended either to discontinue drug or bottle feed
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients with insomnia, anxiety
- Severe or treatment-resistant depression

Potential Disadvantages

- Pediatric and geriatric patients
- Patients concerned with weight gain and sedation

Primary Target Symptoms

- Depressed mood
- Symptoms of anxiety
- Somatic symptoms



Pearls

- ✿ May be more useful than some other TCAs for patients with anxiety, sleep disturbance, and depression with physical illness
- ✿ May be more sedating than some other TCAs
- TCAs are often a first-line treatment option for chronic pain
- TCAs are no longer generally considered a first-line option for depression because of their side effect profile
- TCAs continue to be useful for severe or treatment-resistant depression
- TCAs may aggravate psychotic symptoms
- Alcohol should be avoided because of additive CNS effects
- Underweight patients may be more susceptible to adverse cardiovascular effects
- Children, patients with inadequate hydration, and patients with cardiac disease may be more susceptible to TCA-induced cardiotoxicity than healthy adults
- For the expert only: although generally prohibited, a heroic but potentially dangerous treatment for severely treatment-resistant patients is for an expert to give a tricyclic/tetracyclic

antidepressant other than clomipramine simultaneously with an MAOI for patients who fail to respond to numerous other antidepressants

- If this option is elected, start the MAOI with the tricyclic/tetracyclic antidepressant simultaneously at low doses after appropriate drug washout, then alternately increase doses of these agents every few days to a week as tolerated
- Although very strict dietary and concomitant drug restrictions must be observed to prevent hypertensive crises and serotonin syndrome, the most common side effects of MAOI and tricyclic/tetracyclic antidepressant combinations may be weight gain and orthostatic hypotension
- Patients on tricyclics should be aware that they may experience symptoms such as photosensitivity or blue-green urine
- SSRIs may be more effective than TCAs in women, and TCAs may be more effective than SSRIs in men
- Since tricyclic/tetracyclic antidepressants are substrates for CYP450 2D6, and 7% of the population (especially Caucasians) may have a genetic variant leading to reduced activity of 2D6, such patients may not safely tolerate normal doses of tricyclic/tetracyclic antidepressants and may require dose reduction
- Phenotypic testing may be necessary to detect this genetic variant prior to dosing with a tricyclic/tetracyclic antidepressant, especially in vulnerable populations such as children, elderly, cardiac populations, and those on concomitant medications
- Patients who seem to have extraordinarily severe side effects at normal or low doses may have this phenotypic CYP450 2D6 variant and require low doses or switching to another antidepressant not metabolized by 2D6



Suggested Reading

- Anderson IM. Meta-analytical studies on new antidepressants. *Br Med Bull* 2001;57:161–78.
- Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *J Aff Disorders* 2000;58:19–36.
- Berger M, Gastpar M. Trimipramine: a challenge to current concepts on antidepressives. *Eur Arch Psychiatry Clin Neurosci* 1996;246:235–9.
- Lapierre YD. A review of trimipramine. 30 years of clinical use. *Drugs* 1989;38(Suppl 1):S17–24; discussion S49–50.

THERAPEUTICS

Brands

- Effexor

- Effexor XR

see index for additional brand names

Generic? Yes**Class**

- Neuroscience-based Nomenclature: Serotonin and norepinephrine reuptake inhibitor (SN-RI)
- SNRI (dual serotonin and norepinephrine reuptake inhibitor); often classified as an antidepressant, but it is not just an antidepressant

Commonly Prescribed for

(bold for FDA approved)

- Depression
- Generalized anxiety disorder (GAD)
- Social anxiety disorder (social phobia)
- Panic disorder
- Posttraumatic stress disorder (PTSD)
- Premenstrual dysphoric disorder (PMDD)

**How the Drug Works**

- Boosts neurotransmitters serotonin, norepinephrine/noradrenaline, and dopamine
- Blocks serotonin reuptake pump (serotonin transporter), presumably increasing serotonergic neurotransmission
- Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing noradrenergic neurotransmission
- Presumably desensitizes both serotonin 1A receptors and beta adrenergic receptors
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, venlafaxine can increase dopamine transmission in this part of the brain
- Weakly blocks dopamine reuptake pump (dopamine transporter), and may increase dopamine transmission

How Long Until It Works

- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all

- By contrast, for generalized anxiety, onset of response and increases in remission rates may still occur after 8 weeks, and for up to 6 months after initiating dosing
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Continue treatment until all symptoms are gone (remission), especially in depression and whenever possible in anxiety disorders
- Once symptoms gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders may also need to be indefinite

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some patients who have an initial response may relapse even though they continue treatment, sometimes called "poop-out"
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer

**Best Augmenting Combos for Partial Response or Treatment Resistance**

- Mirtazapine ("California rocket fuel"; a potentially powerful dual serotonin and

norepinephrine combination, but observe for activation of bipolar disorder and suicidal ideation)

- Bupropion, reboxetine, nortriptyline, desipramine, maprotiline, atomoxetine (all potentially powerful enhancers of noradrenergic action, but observe for activation of bipolar disorder and suicidal ideation)
- Modafinil, especially for fatigue, sleepiness, and lack of concentration
- Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression, or treatment-resistant depression
- Benzodiazepines
- If all else fails for anxiety disorders, consider gabapentin or tiagabine
- Hypnotics or trazodone for insomnia
- Classically, lithium, buspirone, or thyroid hormone

Tests

- Check blood pressure before initiating treatment and regularly during treatment

SIDE EFFECTS

How Drug Causes Side Effects

- Theoretically due to increases in serotonin and norepinephrine concentrations at receptors in parts of the brain and body other than those that cause therapeutic actions (e.g., unwanted actions of serotonin in sleep centers causing insomnia, unwanted actions of norepinephrine on acetylcholine release causing constipation and dry mouth, etc.)
- Most side effects are immediate but often go away with time

Notable Side Effects

- Most side effects increase with higher doses, at least transiently
- Headache, nervousness, insomnia, sedation
- Nausea, diarrhea, decreased appetite
- Sexual dysfunction (abnormal ejaculation/orgasm, impotence)
- Asthenia, sweating
- SIADH (syndrome of inappropriate antidiuretic hormone secretion)
- Hyponatremia
- Dose-dependent increase in blood pressure



Life-Threatening or Dangerous Side Effects

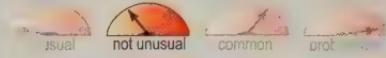
- Rare seizures
- Rare induction of hypomania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

Weight Gain



- Reported but not expected
- Possible weight loss, especially short-term

Sedation



- Occurs in significant minority
- May also be activating in some patients

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- In a few weeks, switch or add other drugs

Best Augmenting Agents for Side Effects

- Often best to try another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
- Trazodone or a hypnotic for insomnia
- Bupropion, sildenafil, vardenafil, or tadalafil for sexual dysfunction
- Benzodiazepines for jitteriness and anxiety, especially at initiation of treatment and especially for anxious patients
- Mirtazapine for insomnia, agitation, and gastrointestinal side effects
- Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition

sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of venlafaxine

DOSING AND USE

Usual Dosage Range

- Depression: 75–225 mg/day, once daily (extended-release) or divided into 2–3 doses (immediate-release)
- GAD: 150–225 mg/day

Dosage Forms

- Capsule (extended-release) 37.5 mg, 75 mg, 150 mg
- Tablet (extended-release) 37.5 mg, 75 mg, 150 mg, 225 mg
- Tablet 25 mg scored, 37.5 mg scored, 50 mg scored, 75 mg scored, 100 mg scored

How to Dose

- Initial dose 37.5 mg once daily (extended-release) or 25–50 mg divided into 2–3 doses (immediate-release) for a week, if tolerated; increase daily dose generally no faster than 75 mg every 4 days until desired efficacy is reached; maximum dose generally 375 mg/day
- Usually try doses at 75 mg increments for a few weeks prior to incrementing by an additional 75 mg



Dosing Tips

- At all doses, potent serotonin reuptake blockade
- 75–225 mg/day may be predominantly serotonergic in some patients, and dual serotonin and norepinephrine acting in other patients
- 225–375 mg/day is dual serotonin and norepinephrine acting in most patients
- Thus, nonresponders at lower doses should try higher doses to be assured of the benefits of dual SNRI action
- At very high doses (e.g., >375 mg/day), dopamine reuptake blocked as well in some patients
- Up to 600 mg/day has been given for heroic cases

- Venlafaxine has an active metabolite O-desmethylvenlafaxine (ODV), which is formed as the result of CYP450 2D6
- Thus, CYP450 2D6 inhibition reduces the formation of ODV, but this is of uncertain clinical significance

Consider checking plasma levels of ODV and venlafaxine in nonresponders who tolerate high doses, and if plasma levels are low, experts can prudently prescribe doses above 375 mg/day while monitoring closely

- Do not break or chew venlafaxine XR capsules, as this will alter controlled-release properties
- For patients with severe problems discontinuing venlafaxine, dosing may need to be tapered over many months (i.e., reduce dose by 1% every 3 days by crushing tablet and suspending or dissolving in 100 mL of fruit juice, and then disposing of 1 mL while drinking the rest; 3–7 days later, dispose of 2 mL, and so on). This is both a form of very slow biological tapering and a form of behavioral desensitization (not for XR)
- For some patients with severe problems discontinuing venlafaxine, it may be useful to add an SSRI with a long half-life, especially fluoxetine, prior to taper of venlafaxine; while maintaining fluoxetine dosing, first slowly taper venlafaxine and then taper fluoxetine
- Be sure to differentiate between reemergence of symptoms requiring reinstitution of treatment and withdrawal symptoms

Overdose

- Can be lethal; may cause no symptoms; possible symptoms include sedation, convulsions, rapid heartbeat
- Fatal toxicity index data from the UK suggest a higher rate of deaths from overdose with venlafaxine than with SSRIs
- Unknown whether this is related to differences in patients who receive venlafaxine or to potential cardiovascular toxicity of venlafaxine

Long-Term Use

- See doctor regularly to monitor blood pressure, especially at doses >225 mg/day

Habit Forming

- No

How to Stop

- Taper to avoid withdrawal effects (dizziness, nausea, stomach cramps, sweating, tingling, dysesthesias)
 - Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation
 - If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly
- * Withdrawal effects can be more common or more severe with venlafaxine than with some other antidepressants

Pharmacokinetics

- Parent drug has 3–7 hour half-life
- Active metabolite has 9–13 hour half-life
- Food does not affect absorption



Drug Interactions

- Tramadol increases the risk of seizures in patients taking an antidepressant
- Can cause a fatal “serotonin syndrome” when combined with MAOIs, so do not use with MAOIs or for at least 14 days after MAOIs are stopped
- Do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing venlafaxine
- Possible increased risk of bleeding, especially when combined with anticoagulants (e.g., warfarin, NSAIDs)
- Concomitant use with cimetidine may reduce clearance of venlafaxine and raise venlafaxine levels
- Could theoretically interfere with the analgesic actions of codeine or possibly with other triptans
- Few known adverse drug interactions



Other Warnings/ Precautions

- Use with caution in patients with history of seizures
- Use with caution in patients with heart disease
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent

- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient has uncontrolled angle-closure glaucoma
- If patient is taking an MAOI
- If there is a proven allergy to venlafaxine

SPECIAL POPULATIONS

Renal Impairment

- Lower dose by 25–50%
- Patients on dialysis should not receive subsequent dose until dialysis is completed

Hepatic Impairment

- Lower dose by 50%

Cardiac Impairment

- Drug should be used with caution
- Hypertension should be controlled prior to initiation of venlafaxine and should be monitored regularly during treatment
- Venlafaxine has a dose-dependent effect on increasing blood pressure
- Venlafaxine is contraindicated in patients with heart disease in the UK
- Venlafaxine can block cardiac ion channels *in vitro*
- Venlafaxine worsens (i.e., reduces) heart rate variability in depression, perhaps due to norepinephrine reuptake inhibition

Elderly

- Some patients may tolerate lower doses better
- Risk of SIADH with SSRIs is higher in the elderly
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Not specifically approved, but preliminary data suggest that venlafaxine is effective in children and adolescents with depression, anxiety disorders, and ADHD



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester
- Nonetheless, continuous treatment during pregnancy may be necessary and has not been proven to be harmful to the fetus
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy
- Neonates exposed to SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding; reported symptoms are consistent with either a direct toxic

effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome, and include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying

Breast Feeding

- Some drug is found in mother's breast milk
- Trace amounts may be present in nursing children whose mothers are on venlafaxine
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients, this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients with retarded depression
- Patients with atypical depression
- Patients with comorbid anxiety
- Patients with depression may have higher remission rates on SNRIs than on SSRIs
- Depressed patients with somatic symptoms, fatigue, and pain
- Patients who do not respond or remit on treatment with SSRIs

Potential Disadvantages

- Patients sensitive to nausea
- Patients with borderline or uncontrolled hypertension
- Patients with cardiac disease

Primary Target Symptoms

- Depressed mood
- Energy, motivation, and interest
- Sleep disturbance
- Anxiety



Pearls

- ✿ May be effective in patients who fail to respond to SSRIs, and may be one of the preferred treatments for treatment-resistant depression
- ✿ May be used in combination with other antidepressants for treatment-refractory cases
- XR formulation improves tolerability, reduces nausea, and requires only once daily dosing
- May be effective in a broad array of anxiety disorders
- May be effective in adult ADHD
- Not studied in stress urinary incontinence
- ✿ Has greater potency for serotonin reuptake blockade than for norepinephrine reuptake blockade, but this is of unclear clinical significance as a differentiating feature from other SNRIs
- ✿ In vitro binding studies tend to underestimate in vivo potency for reuptake blockade, as they do not factor in the presence of high concentrations of an active metabolite, higher oral mg dosing, or the lower protein binding which can increase functional drug levels at receptor sites

- Effective dose range is broad (i.e., 75–375 mg in many difficult cases, and up to 600 mg or more in heroic cases)
- ✿ Preliminary studies in neuropathic pain and fibromyalgia suggest potential efficacy
- Efficacy as well as side effects (especially nausea and increased blood pressure) are dose-dependent
- Blood pressure increases rare for XR formulation in doses up to 225 mg
- More withdrawal reactions reported upon discontinuation than for some other antidepressants
- May be helpful for hot flushes in perimenopausal women
- May be associated with higher depression remission rates than SSRIs
- ✿ Because of recent studies from the UK that suggest a higher rate of deaths from overdose with venlafaxine than with SSRIs, and because of its potential to affect heart function, venlafaxine can only be prescribed in the UK by specialist doctors and is contraindicated there in patients with heart disease
- Overdose data are from fatal toxicity index studies, which do not take into account patient characteristics or whether drug use was first- or second-line
- Venlafaxine's toxicity in overdose is less than that for TCAs



Suggested Reading

Buckley NA, McManus PR. Fatal toxicity of serotonergic and other antidepressant drugs: analysis of United Kingdom mortality data. *BMJ* 2002;325:1332–3.

Cheeta S, Schifano F, Oyefeso A, Webb L, Ghodse AH. Antidepressant-related deaths and antidepressant prescriptions in England and Wales, 1998–2000. *Br J Psychiatry* 2004;184:41–7.

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THERAPEUTICS

Brands • Viibryd

see index for additional brand names

Generic? No**Class**

- Neuroscience-based Nomenclature: serotonin multimodal (S-MM)
- SPARI (serotonin partial agonist reuptake inhibitor)
- Dual-acting serotonin reuptake inhibitor plus 5HT1A partial agonist

Commonly Prescribed for

(bold for FDA approved)

- Major depressive disorder
- Anxiety
- Obsessive compulsive disorder

**How the Drug Works**

- Boosts neurotransmitter serotonin
- Blocks serotonin reuptake pump (serotonin transporter)
- Desensitizes serotonin receptors, especially serotonin 1A autoreceptors
- Presumably increases serotonergic neurotransmission
- Partial agonist actions at presynaptic somatodendritic serotonin 1A autoreceptors may theoretically enhance serotonergic activity and contribute to antidepressant actions
- Partial agonist actions at postsynaptic serotonin 1A receptors may theoretically diminish sexual dysfunction caused by serotonin reuptake inhibition

How Long Until It Works

- Onset of therapeutic actions may be sooner than with other SSRIs due to vilazodone's actions at serotonin 1A receptors, with current data suggesting onset of efficacy as early as week 1, despite the fact that standard titration does not arrive at full therapeutic dose of 40 mg until the third week
- If it is not working within 6 or 8 weeks, it may require a dosage increase (off label) or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Continue treatment until all symptoms are gone (remission) or significantly reduced
- Once symptoms gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders may also need to be indefinite

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some patients who have an initial response may relapse even though they continue treatment, sometimes called "poop-out"
- Consider increasing dose to 50–80 mg/day "off label" over several weeks if tolerated
- Consider switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and switch to a mood stabilizer

**Best Augmenting Combos for Partial Response or Treatment Resistance**

- Trazodone, especially for insomnia
- Bupropion, mirtazapine, reboxetine, or atomoxetine (use combinations of antidepressants with caution as this may activate bipolar disorder and suicidal ideation)
- Modafinil, especially for fatigue, sleepiness, and lack of concentration

- Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression, treatment-resistant depression, or treatment-resistant anxiety disorders
- Benzodiazepines
- If all else fails for anxiety disorders, consider gabapentin, pregabalin, or tiagabine
- Hypnotics for insomnia
- Classically, lithium, buspirone, or thyroid hormone

Tests

- None for healthy individuals

SIDE EFFECTS

How Drug Causes Side Effects

- Theoretically due to increases in serotonin concentrations at serotonin receptors in parts of the brain and body other than those that cause therapeutic actions (e.g., unwanted actions of serotonin in sleep centers causing insomnia, unwanted actions of serotonin in the gut causing diarrhea, etc.)
- Increasing serotonin can cause diminished dopamine release and might contribute to emotional flattening, cognitive slowing, and apathy in some patients
- Most side effects are immediate but often go away with time, in contrast to most therapeutic effects, which are delayed and are enhanced over time

Notable Side Effects

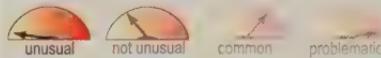
- Nausea, diarrhea, vomiting
- Insomnia, dizziness
- Note: patients with diagnosed or undiagnosed bipolar or psychotic disorders may be more vulnerable to CNS-activating actions of serotonergic antidepressants
- Bruising and rare bleeding
- Rare hyponatremia (mostly in elderly patients and generally reversible on discontinuation of vilazodone)
- Sexual dysfunction (men: delayed ejaculation; men and women: decreased sexual desire, anorgasmia) slightly greater than placebo and generally less than for SSRIs/SNRIs, but no head-to-head studies
- SIADH (syndrome of inappropriate antiuretic hormone secretion)



Life-Threatening or Dangerous Side Effects

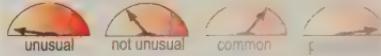
- Rare seizures
- Rare induction of mania and activation of suicidal ideation

Weight Gain



- Reported but not expected

Sedation



- Reported but not expected

What to Do About Side Effects

- Wait
- Wait
- Wait
- In a few weeks, switch to another agent or add other drugs

Best Augmenting Agents for Side Effects

- Often best to try another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
- Trazodone or a hypnotic for insomnia
- Bupropion, sildenafil, vardenafil, or tadalafil for sexual dysfunction
- Bupropion for emotional flattening, cognitive slowing, or apathy
- Mirtazapine for insomnia, agitation, and gastrointestinal side effects
- Benzodiazepines for jitteriness and anxiety, especially at initiation of treatment and especially for anxious patients
- Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of vilazodone

DOSING AND USE

Usual Dosage Range

- 20–40 mg/day

Dosage Forms

- Tablets 10 mg, 20 mg, 40 mg

How To Dose

- Initial 10 mg/day; increase to 20 mg/day after one week; can increase to 40 mg/day after one more week; should be taken with food



Dosing Tips

- Given once daily, any time of day tolerated but must be administered with food, because taking on an empty stomach may reduce absorption of vilazodone by 50%
- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activating a bipolar disorder and switch to a mood stabilizer or an atypical antipsychotic
- No minimally effective dose has been established, so theoretically possible that doses lower than 40 mg daily may be effective in some patients
- Doses higher than 40 mg daily have not been well studied, but theoretically possible that slow titration to doses higher than 40 mg may be effective in some patients, particularly those with treatment-resistant depression who fail to respond adequately to 40 mg daily

Overdose

- Few reports of vilazodone overdose
- No fatalities; serotonin syndrome, lethargy, restlessness, hallucinations, disorientation

Long-Term Use

- Has not been evaluated in controlled studies, but long-term treatment of major depressive disorder is generally necessary

Habit Forming

- No

How to Stop

- Tapering to avoid potential withdrawal reactions generally prudent
- Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation

- If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly

Pharmacokinetics

- Mean terminal half-life 25 hours
- Metabolized by CYP450 3A4
- Absorption and bioavailability are reduced by half when taken on an empty stomach



Drug Interactions

- Tramadol increases the risk of seizures in patients taking an antidepressant
- Can cause a fatal “serotonin syndrome” when combined with MAOIs, so do not use with MAOIs or for at least 14 days after MAOIs are stopped
- Do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing vilazodone
- Inhibitors of CYP450 3A4, such as nefazodone, fluoxetine, fluvoxamine, and even grapefruit juice, may decrease the clearance of vilazodone and thereby raise its plasma levels, so dose should be reduced to 20 mg when coadministered with strong CYP3A4 inhibitors
- Inducers of CYP450 3A4, such as carbamazepine, may increase clearance of vilazodone and thus lower its plasma levels and possibly reduce therapeutic effects
- Could theoretically cause weakness, hyperreflexia, and incoordination when combined with sumatriptan or possibly other triptans, requiring careful monitoring of patient
- Possible increased risk of bleeding, especially when combined with anticoagulants (e.g., warfarin, NSAIDs)



Other Warnings/ Precautions

- Use with caution in patients with history of seizure
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- Not approved in children, so when treating children off label, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and

make sure to document this in the patient's chart

- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is taking an MAOI
- If there is a proven allergy to vilazodone

SPECIAL POPULATIONS

Renal Impairment

- No dose adjustment necessary

Hepatic Impairment

- No dose adjustment necessary for mild to moderate impairment
- Has not been studied in patients with severe hepatic impairment

Cardiac Impairment

- Not systematically evaluated in patients with cardiac impairment
- Vilazodone has not shown any significant effect on blood pressure, heart rate, or QT interval in placebo-controlled trials
- Treating depression with SSRIs in patients with acute angina or following myocardial infarction may reduce cardiac events and improve survival as well as mood

Elderly

- No dose adjustment necessary
- Some patients may tolerate lower doses better
- Risk of SIADH with SSRIs is higher in the elderly
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Safety and efficacy have not been established

- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and strongly consider informing parents or guardians of this risk so they can help observe child or adolescent patients



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester
- Nonetheless, continuous treatment during pregnancy may be necessary and has not been proven to be harmful to the fetus
- At delivery there may be more bleeding in the mother and transient irritability or sedation in the newborn
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients, this may mean continuing treatment during pregnancy
- Exposure to serotonin reuptake inhibitors early in pregnancy may be associated with increased risk of septal heart defects (absolute risk is small)
- Serotonin reuptake inhibitor use beyond the 20th week of pregnancy may be associated with increased risk of pulmonary hypertension in newborns, although this is not proven
- Exposure to serotonin reuptake inhibitors late in pregnancy may be associated with increased risk of gestational hypertension and preeclampsia
- Neonates exposed to SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged

hospitalization, respiratory support, and tube feeding; reported symptoms are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome, and include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying.

Breast Feeding

- Unknown if vilazodone is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- Trace amounts may be present in nursing children whose mothers are on vilazodone
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients, this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients with sexual dysfunction on an SSRI/SNRI or who wish to avoid sexual dysfunction on an antidepressant
- Patients with weight gain on another antidepressant or who wish to avoid weight gain on an antidepressant
- Patients with mixed anxiety and depression

Potential Disadvantages

- Patients who cannot take medication reliably with food
- Patients sensitive to gastrointestinal side effects such as diarrhea and nausea

Primary Target Symptoms

- Depressed mood
- Anxiety



Pearls

- Serotonin 1A partial agonist property is a relatively unique mechanism of action among approved antidepressants (also vortioxetine and atypical antipsychotic augmenting agents such as quetiapine, aripiprazole, brexpiprazole, and others)
- First member of a new antidepressant class, SPARIs, or serotonin partial agonist reuptake inhibitors
- Relative lack of sexual dysfunction and weight gain compared to many other antidepressants that block serotonin reuptake may be due to the serotonin 1A partial agonist properties of vilazodone
- High doses would theoretically raise brain serotonin levels more robustly than the standard dose, and may improve efficacy in some patients but reduce tolerability in some patients
- Consider doses of 50–80 mg daily if effective and well tolerated for patients with treatment-resistant depression or treatment-resistant OCD and other anxiety disorders
- Consider for patients with comorbid anxiety disorders plus depression
- Nonresponse to vilazodone in elderly may require consideration of mild cognitive impairment or Alzheimer disease



Suggested Reading

Citrome L. Vilazodone for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant – what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *Int J Clin Pract* 2012;66(4):356–68.

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THERAPEUTICS

Brands • Trintellix (formerly Brintellix)
see index for additional brand names

Generic? No



Class

- Neuroscience-based Nomenclature: serotonin multimodal (S-MM)
- Multimodal antidepressant

Commonly Prescribed for

(bold for FDA approved)

- **Major depressive disorder**
- Generalized anxiety disorder (GAD)
- Cognitive symptoms associated with depression
- Geriatric depression



How the Drug Works

- Increases release of several different neurotransmitters (serotonin, norepinephrine, dopamine, glutamate, acetylcholine, and histamine) and reduces the release of GABA through 3 different modes of action
- Mode 1: blocks serotonin reuptake pump (serotonin transporter)
- Mode 2: binds to G protein-linked receptors (full agonist at serotonin 1A receptors, partial agonist at serotonin 1B receptors, antagonist at serotonin 1D and serotonin 7 receptors)
- Mode 3: binds to ion channel-linked receptors (antagonist at serotonin 3 receptors)
- Full agonist actions at presynaptic somatodendritic serotonin 1A autoreceptors may theoretically enhance serotonergic activity and contribute to antidepressant actions
- Full agonist actions at postsynaptic serotonin 1A receptors may theoretically diminish sexual dysfunction caused by serotonin reuptake inhibition
- Antagonist actions at serotonin 3 receptors may theoretically enhance noradrenergic, acetylcholinergic, and glutamatergic activity and contribute to antidepressant and pro-cognitive actions
- Antagonist actions at serotonin 3 receptors may theoretically reduce nausea and

vomiting caused by serotonin reuptake inhibition

- Antagonist actions at serotonin 7 receptors may theoretically contribute to antidepressant and pro-cognitive actions as well as reduce insomnia caused by serotonin reuptake inhibition
- Partial agonist actions at serotonin 1B receptors may enhance not only serotonin release, but also acetylcholine and histamine release
- Antagonist actions at serotonin 1D receptors may enhance serotonin release and may also theoretically enhance the release of pro-cognitive neurotransmitters and thereby enhance pro-cognitive actions

How Long Until It Works

- Onset of therapeutic actions is usually not immediate, but often delayed 2–4 weeks
- However, vortioxetine has a specific claim of onset of action at week 2
- If it is not working within 6 or 8 weeks, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Continue treatment until all symptoms are gone (remission) or significantly reduced
- Once symptoms gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in anxiety disorders may also need to be indefinite

If It Doesn't Work

- Many patients only have a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)

- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some patients who have an initial response may relapse even though they continue treatment, sometimes called “poop-out”
- Consider switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and switch to a mood stabilizer



Best Augmenting Combos for Partial Response or Treatment Resistance

- Augmentation experience is limited compared to other antidepressants
- Trazodone, especially for insomnia
- Bupropion, mirtazapine, reboxetine, or atomoxetine (use combinations of antidepressants with caution as this may activate bipolar disorder and suicidal ideation)
- Use with caution with antidepressants that are CYP450 2D6 inhibitors (e.g., bupropion, duloxetine, fluoxetine, paroxetine), as these agents will increase vortioxetine levels and may require a dose reduction of vortioxetine
- Modafinil, especially for fatigue, sleepiness, and lack of concentration
- Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression, treatment-resistant depression, or treatment-resistant anxiety disorders
- Benzodiazepines
- If all else fails for anxiety disorders, consider gabapentin, pregabalin, or tiagabine
- Hypnotics for insomnia
- Classically, lithium, buspirone, or thyroid hormone

Tests

- None for healthy individuals

SIDE EFFECTS

How Drug Causes Side Effects

- Theoretically due to increases in serotonin concentrations at serotonin receptors in parts of the brain and body other than those that cause therapeutic actions (e.g., unwanted actions of serotonin at central serotonin 1A receptors causing nausea, unwanted actions of serotonin in the CNS causing sexual dysfunction, etc.)
- Most side effects are immediate but often go away with time, in contrast to most therapeutic effects, which are delayed and are enhanced over time

Notable Side Effects

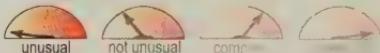
- Nausea, vomiting, constipation
- Sexual dysfunction



Life-Threatening or Dangerous Side Effects

- Rare seizures
- Rare induction of mania and activation of suicidal ideation

Weight Gain



- Reported but not expected

Sedation



- Reported but not expected

What to Do About Side Effects

- Wait
- Wait
- Wait
- In a few weeks, switch to another agent or add other drugs

Best Augmenting Agents for Side Effects

- Often best to try another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
- Trazodone or a hypnotic for insomnia

- Sildenafil, vardenafil, or tadalafil for sexual dysfunction
- Bupropion for emotional flattening, cognitive slowing, apathy, or sexual dysfunction (with caution, as bupropion can raise vortioxetine levels via CYP450 2D6 inhibition)
- Mirtazapine for insomnia, agitation, and gastrointestinal side effects
- Benzodiazepines for jitteriness and anxiety, especially at initiation of treatment and especially for anxious patients
- Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer, or an atypical antipsychotic, and/or discontinuation of vortioxetine

DOSING AND USE

Usual Dosage Range

- 5–20 mg/day

Dosage Forms

- Tablet 5 mg, 10 mg, 15 mg, 20 mg

How to Dose

- Initial 10 mg once daily; can decrease to 5 mg once daily or increase to 20 mg once daily depending on patient response; maximum recommended dose generally 20 mg once daily



Dosing Tips

- Can be taken with or without food
- Tablet should not be divided, crushed, or dissolved
- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation,

consider the possibility of activating a bipolar disorder and switch to a mood stabilizer or an atypical antipsychotic

Overdose

- No fatalities have been reported; nausea, dizziness, diarrhea, abdominal discomfort, generalized pruritus, somnolence, flushing

Long-Term Use

- Long-term treatment of major depressive disorder is generally necessary

Habit Forming

- No

How to Stop

- Taper not necessary with recommended doses

Pharmacokinetics

- Metabolized by CYP450 2D6, 3A4/5, 2C19, 2C9, 2A6, 2C8, and 2B6
- Mean terminal half-life approximately 66 hours



Drug Interactions

- Tramadol increases the risk of seizures in patients taking an antidepressant
- Can cause a fatal “serotonin syndrome” when combined with MAOIs, so do not use with MAOIs or for at least 14–21 days after MAOIs are stopped
- Do not start an MAOI for at least 5 half-lives (about 14 days for vortioxetine with a half-life of 66 hours) after discontinuing vortioxetine
- Strong CYP450 2D6 inhibitors can increase plasma levels of vortioxetine, possibly requiring its dose to be decreased
- Broad CYP450 2D6 inducers can decrease plasma levels of vortioxetine, possibly requiring its dose to be increased
- Could theoretically cause weakness, hyperreflexia, and incoordination when combined with sumatriptan or possibly other triptans, requiring careful monitoring of patient
- Possible increased risk of bleeding, especially when combined with anticoagulants (e.g., warfarin, NSAIDs)



Other Warnings/ Precautions

- Use with caution in patients with history of seizures
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- Possible risk of hyponatremia related to SIADH (syndrome of inappropriate antidiuretic hormone secretion) with serotonergic drugs
- Not approved in children, so when treating children off label, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of non-treatment with antidepressants and make sure to document this in the patient's chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is taking an MAOI
- If there is a proven allergy to vortioxetine

SPECIAL POPULATIONS

Renal Impairment

- No dose adjustment necessary

Hepatic Impairment

- No dose adjustment necessary for mild to moderate impairment
- Has not been studied in patients with severe hepatic impairment

Cardiac Impairment

- Not systematically evaluated in patients with cardiac impairment
- Treating depression with SSRIs in patients with acute angina or following myocardial infarction may reduce cardiac events and improve survival as well as mood; not known for vortioxetine

Elderly

- No dose adjustment necessary
- Some patients may tolerate lower doses better
- Risk of SIADH with SSRIs is higher in the elderly
- Reduction in risk of suicidality with antidepressants compared to placebo in adults age 65 and older



Children and Adolescents

- Safety and efficacy have not been established
- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and strongly consider informing parents or guardian of this risk so they can help observe child or adolescent patients



Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester
- Nonetheless, continuous treatment during pregnancy may be necessary and has not been proven to be harmful to the fetus
- At delivery there may be more bleeding in the mother and transient irritability or sedation in the newborn
- Must weigh the risk of treatment (first trimester fetal development, third trimester

newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child

- For many patients, this may mean continuing treatment during pregnancy
- Exposure to serotonin reuptake inhibitors early in pregnancy may be associated with increased risk of septal heart defects (absolute risk is small)
- Use of serotonin reuptake inhibitors beyond the 20th week of pregnancy may be associated with increased risk of pulmonary hypertension in newborns, although this is not proven
- Exposure to serotonin reuptake inhibitors late in pregnancy may be associated with increased risk of gestational hypertension and preeclampsia
- Neonates exposed to SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding; reported symptoms are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome, and include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying

Breast Feeding

- Unknown if vortioxetine is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients, this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients with sexual dysfunction
- Patients with cognitive symptoms of depression
- Patients with residual cognitive symptoms after treatment with another antidepressant
- Elderly patients
- Patients who have not responded to other antidepressants
- Patients who do not want weight gain

Potential Disadvantages

- Cost

Primary Target Symptoms

- Depressed mood
- Cognitive symptoms
- Anxiety



Pearls

- In May 2016 the US FDA approved a brand name change from Brintellix to Trintellix in order to decrease prescribing and dispensing errors due to name confusion with the anti-platelet medication Brilinta (ticagrelor)
- May have less sexual dysfunction than SSRIs
- Multiple studies show pro-cognitive effects greater than a comparator antidepressant in patients with major depressive episodes
- Patients who do not respond to antidepressants with other mechanisms of action may respond to vortioxetine
- Shown effective specifically in elderly patients with depression, with a positive trial in geriatric depression with improvement of cognition as well as mood
- Has a unique claim of preventing recurrences in major depression
- No weight gain in clinical trials
- Long half-life means vortioxetine can generally be abruptly discontinued, although some caution may be necessary when stopping higher doses (i.e., 15 or 20 mg/day)
- Despite serotonin 3 antagonist actions, nausea is common, presumably due to full agonist actions at serotonin 1A receptors
- Dose response for efficacy in depression: higher doses are more effective
- Vortioxetine has a unique multimodal mechanism of action
- Nonresponse to vortioxetine in elderly may require consideration of mild cognitive impairment or Alzheimer disease



Suggested Reading

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Abbreviations

5HT	serotonin
ACh	acetylcholine
AChE	acetylcholinesterase
ADHD	attention deficit hyperactivity disorder
AE	adverse effect
ALPT	total serum alkaline phosphatase
ALT	alanine aminotransferase
AMPA	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ANA	antinuclear antibody
ANC	Absolute neutrophil count
AST	aspartate aminotransferase
BEN	benign ethnic neutropenia
BHB	beta-hydroxybutyric acid
bid	twice a day
BMI	body mass index
BP	blood pressure
BuChE	butyrylcholinesterase
CBC	complete blood count
CR	controlled-release
CRP	C-reactive protein
CSF	cerebrospinal fluid
CMI	clomipramine
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CYP450	cytochrome P450
DA	dopamine
De-CMI	desmethyl-clomipramine
dL	deciliter
DLB	dementia with Lewy bodies
ECG	electrocardiogram
EEG	electroencephalogram
EKG	electrocardiogram
EPS	extrapyramidal side effects
ER	extended-release
FDA	Food and Drug Administration
GABA	gamma-aminobutyric acid
GAD	generalized anxiety disorder

GFR	glomerular filtration rate
HDL	high-density lipoprotein
HMG CoA	beta-hydroxy-beta-methylglutaryl coenzyme A
IM	intramuscular
IR	immediate-release
IV	intravenous
LAI	long-acting injectable
lb	pound
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitor
mCPP	meta-chloro-phenyl-piperazine
MDMA	3,4-methylenedioxymethamphetamine (ecstasy)
mg	milligram
mL	milliliter
mmHg	millimeters of mercury
MRI	magnetic resonance imaging
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
NE	norepinephrine
NET	norepinephrine transporter
NMDA	<i>N</i> -methyl-D-aspartate
NSAID	nonsteroidal anti-inflammatory drug
OCD	obsessive-compulsive disorder
ODT	oral disintegrating tablet
ODV	O-desmethylvenlafaxine
OSAHS	obstructive sleep apnea/hypopnea syndrome
PBA	pseudobulbar affect
PCP	phencyclidine
PET	positron emission tomography
PMDD	premenstrual dysphoric disorder
prn	as needed
PTSD	posttraumatic stress disorder
qd	once a day
qhs	once a day at bedtime
qid	4 times a day
RIMA	reversible inhibitor of monoamine oxidase A
SGRI	selective GABA reuptake inhibitor
SNRI	dual serotonin and norepinephrine reuptake inhibitor
SPARI	serotonin partial antagonist reuptake inhibitor
SR	sustained release

SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
tid	3 times a day
TSH	thyroid-stimulating hormone
VMA	vanillylmandelic acid
WBC	white blood cell count

Stahl's Essential Psychopharmacology



Stephen M. Stahl, MD, PhD is Associate Professor of Psychiatry at UC San Diego, Honorary Visiting Senior Fellow University of Cambridge, UK, and Chairman of the Neuroscience Education Institute, California. He has conducted numerous research projects funded by the National Institute of Mental Health, the Veterans Administration, and pharmaceutical industry. The author of more than 100 articles and chapters, Dr Stahl is an internationally recognized clinician, teacher, and lecturer in psychiatry with subspecialty interests in psychopharmacology.



The Essential Psychopharmacology franchise began over 20 years ago as a published offshoot of my lectures for mental health professionals.

I have always had to 'see' something before I could understand it, especially disease mechanisms and drug actions, and thus developed a compendium of figures and diagrams for my lectures. With my long term illustrator Nancy Munther, we gradually developed a 'visual language' for psychopharmacology with icons and figures that have become the signature feature of *Stahl's Essential Psychopharmacology*.

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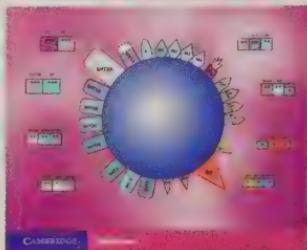
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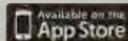
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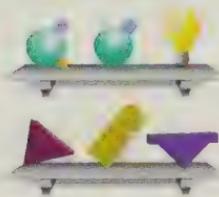
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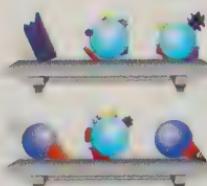
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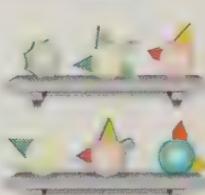
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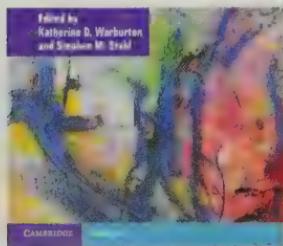
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Katherine D. Warburton, University of California, Davis, Stephen M. Stahl,
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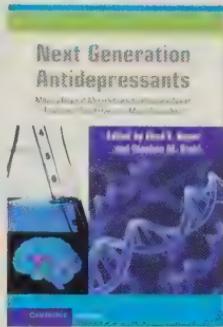
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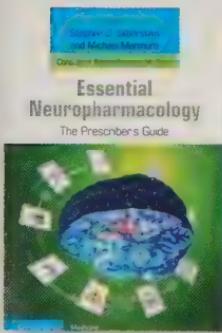
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Stephen D Silberstein, MD and Michael J Marmura, MD, Jefferson Medical College, Philadelphia, USA, Stephen M Stahl, MD, PhD, University of California, San Diego, USA, University of Cambridge, UK

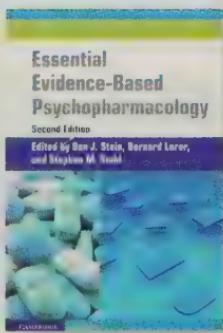
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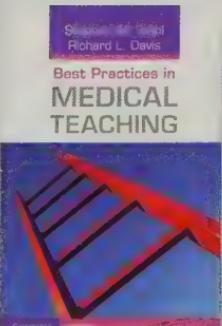
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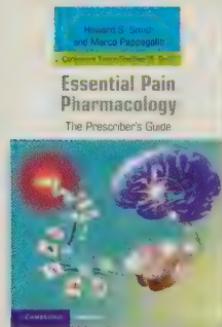
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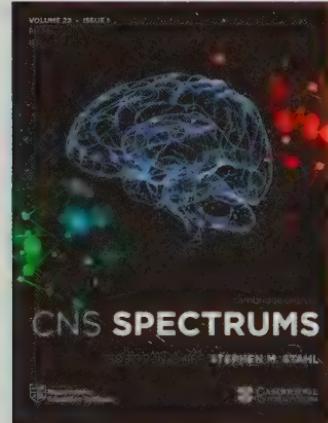
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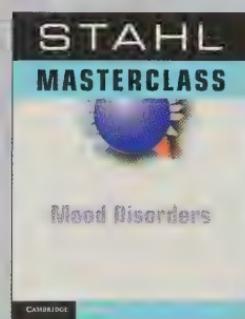
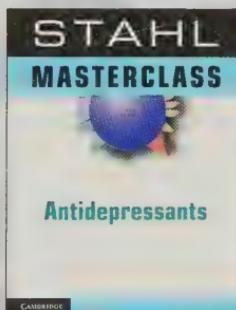
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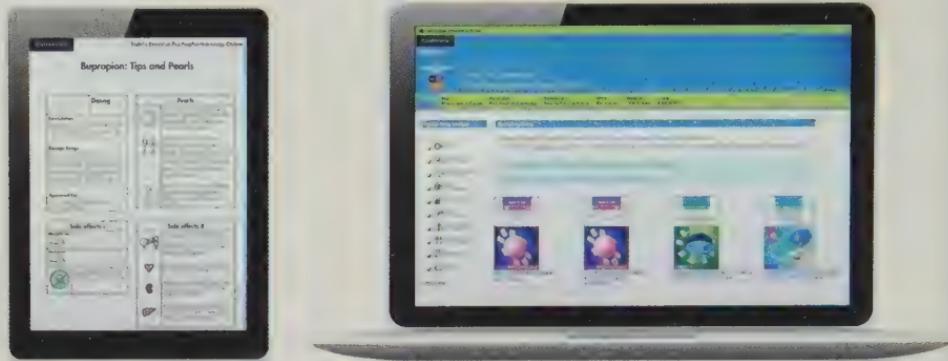
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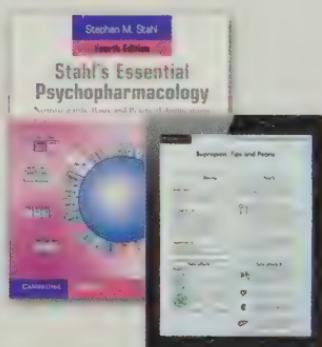
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Stephen M. Stahl is Adjunct Professor of Psychiatry at the University of California, San Diego, and Honorary Visiting Senior Fellow at the University of Cambridge, UK. He has conducted various research projects awarded by the National Institute of Mental Health, Veteran's Affairs, and the pharmaceutical industry. Author of more than 500 articles and chapters, Dr Stahl is also the author of the bestseller *Stahl's Essential Psychopharmacology*.

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