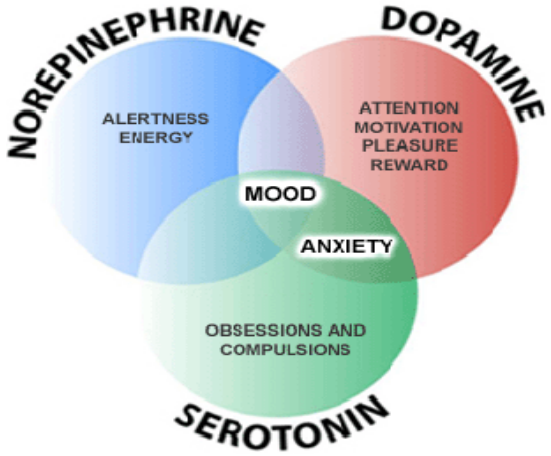


Antidepressant pharmacology

Phychoenergetics, Timoanaleptics

Types of depression

- Unipolar – bipolar
- Unipolar: 1. Major 2. Minor (dysthimic disorder)

Antidepressants are used

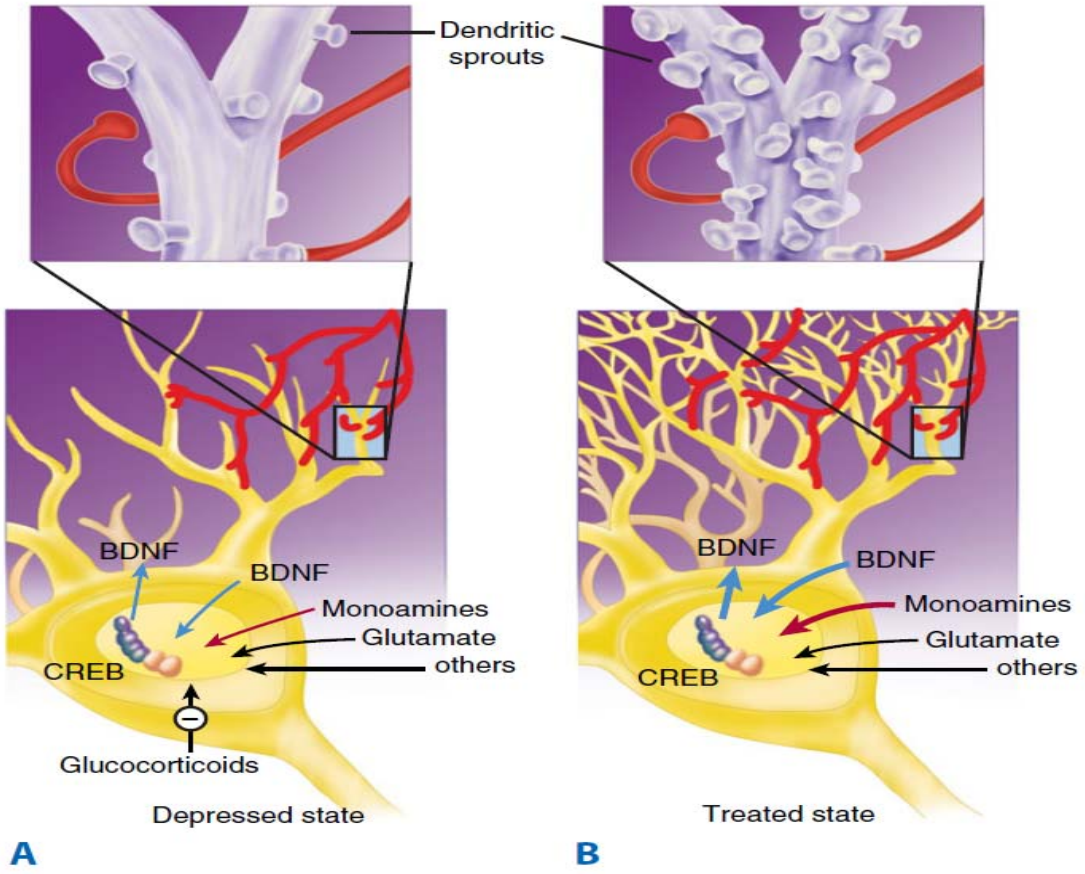
- MDD (Major Depressive Disorder)
- Panic disorder
- GAD (Generalized Anxiety Disorder
- PTSD (PostTraumatic Stress Disorder)
- OCD (Obsessive-Compulsive Disorder)
- Neuropathic pain
- Fibromyalgia

Theories of depression

- Neurotrophic hypothesis (BDNF, trkB)
- Monoamine theory
  - MHPG (3-methoxy-4-hydroxyphenylglycol)
  - 5-HIAA (5-hydroxy-indol-acetic acid)

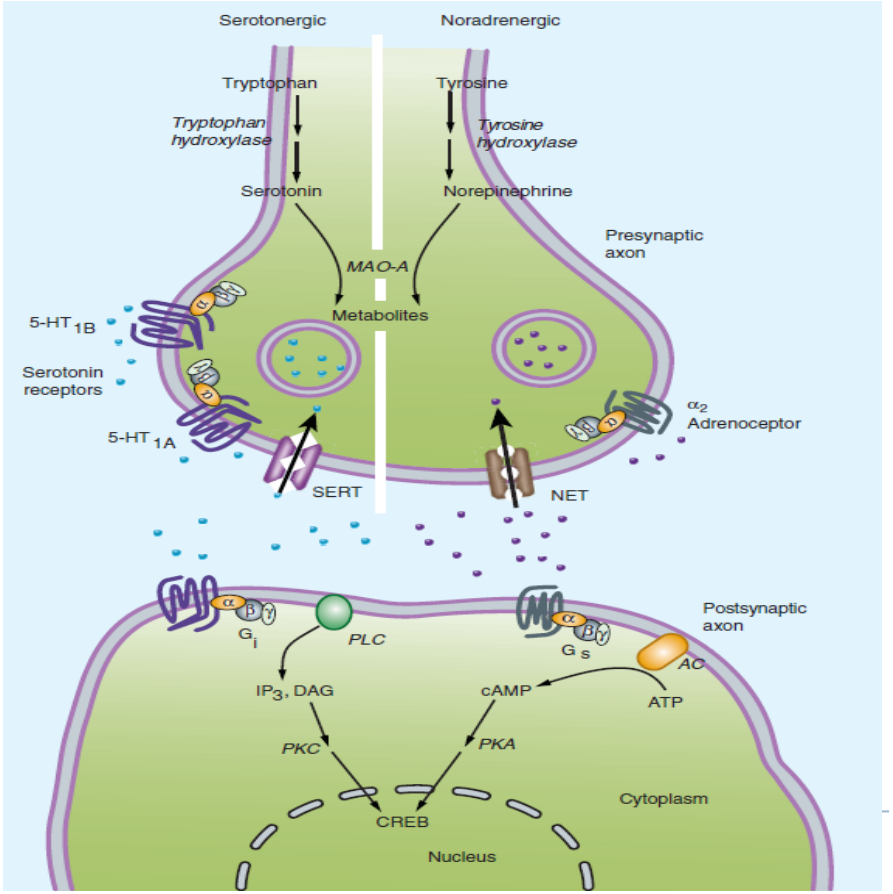
Dexamethasone suppression test negative!

Neurotrophic hypothesis



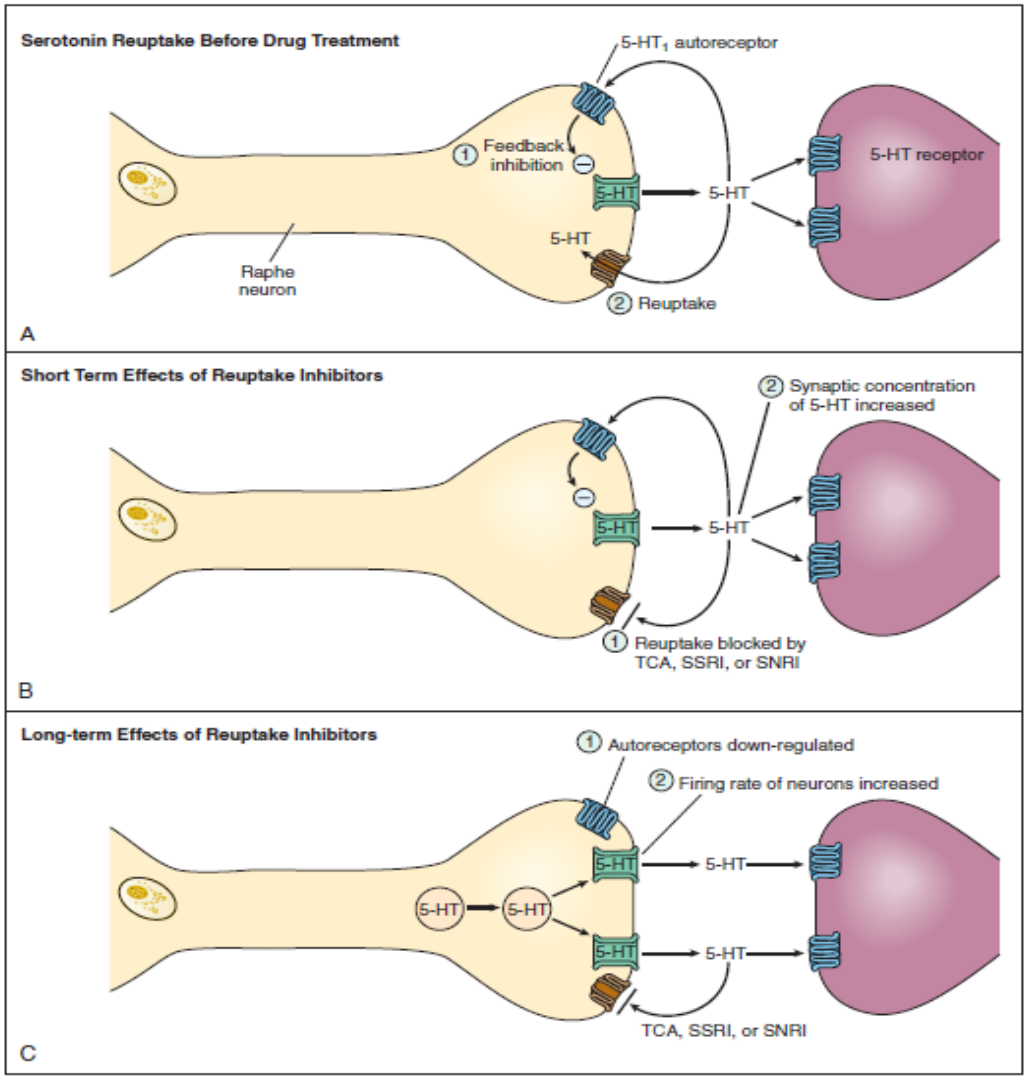
The neurotrophic hypothesis of major depression. Changes in trophic factors (especially brain-derived neurotrophic factor, BDNF) and hormones appear to play a major role in the development of major depression (**A).**
Successful treatment results in changes in these factors (**B). CREB, cAMP response element-binding (protein). BDNF, brain-derived neurotrophic factor.**

Monoamine theory (Schildkraut, 1965)

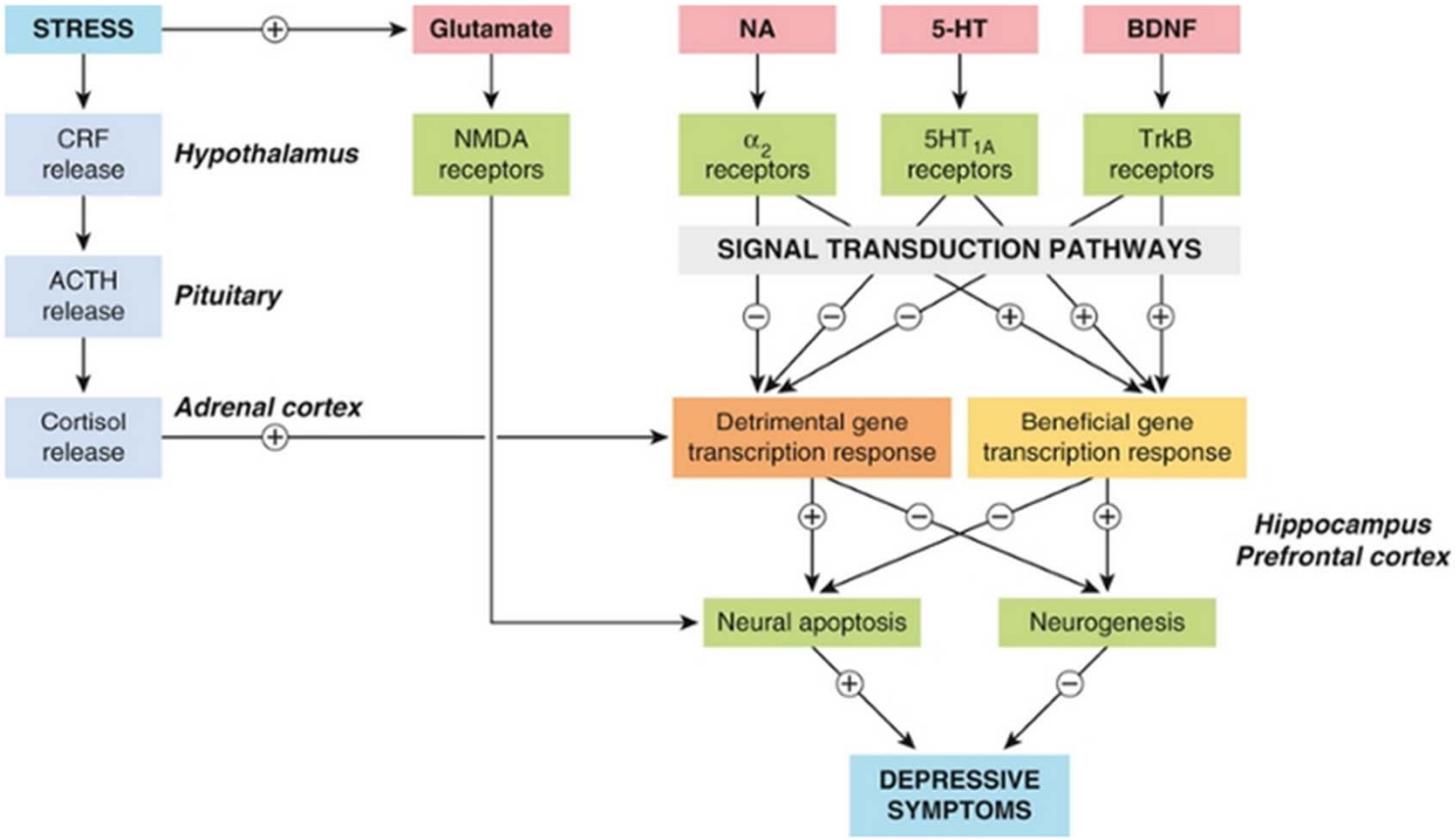


The amine hypothesis of major depression. Depression appears to be associated with changes in serotonin or norepinephrine signaling in the brain (or both) with significant downstream effects. Most antidepressants cause changes in amine signaling.

AC, adenylyl cyclase; 5-HT, serotonin; CREB, cAMP response element-binding (protein); DAG, diacyl glycerol; IP_3, inositol trisphosphate; MAO, monoamine oxidase; NET, norepinephrine transporter; PKC, protein kinase C; PLC, phospholipase C; SERT, serotonin transporter.


Serotonin Reuptake Before Drug Treatment
5-HT1 autoreceptor
1 Feedback inhibition
5-HT
5-HT
5-HT receptor
5-HT
Raphe neuron
2 Reuptake
A
Short Term Effects of Reuptake Inhibitors
2 Synaptic concentration of 5-HT increased
5-HT
5-HT
1 Reuptake blocked by TCA, SSRI, or SNRI
B
Long-term Effects of Reuptake Inhibitors
1 Autoreceptors down-regulated
2 Firing rate of neurons increased
5-HT
5-HT
5-HT
5-HT
5-HT
5-HT
TCA, SSRI, or SNRI
C

Depression mechanisms



Animal models

- Learned Helplessness: Delivery of repeated inescapeable painful stimuli)
- Mother-infant separation
- Reserpine

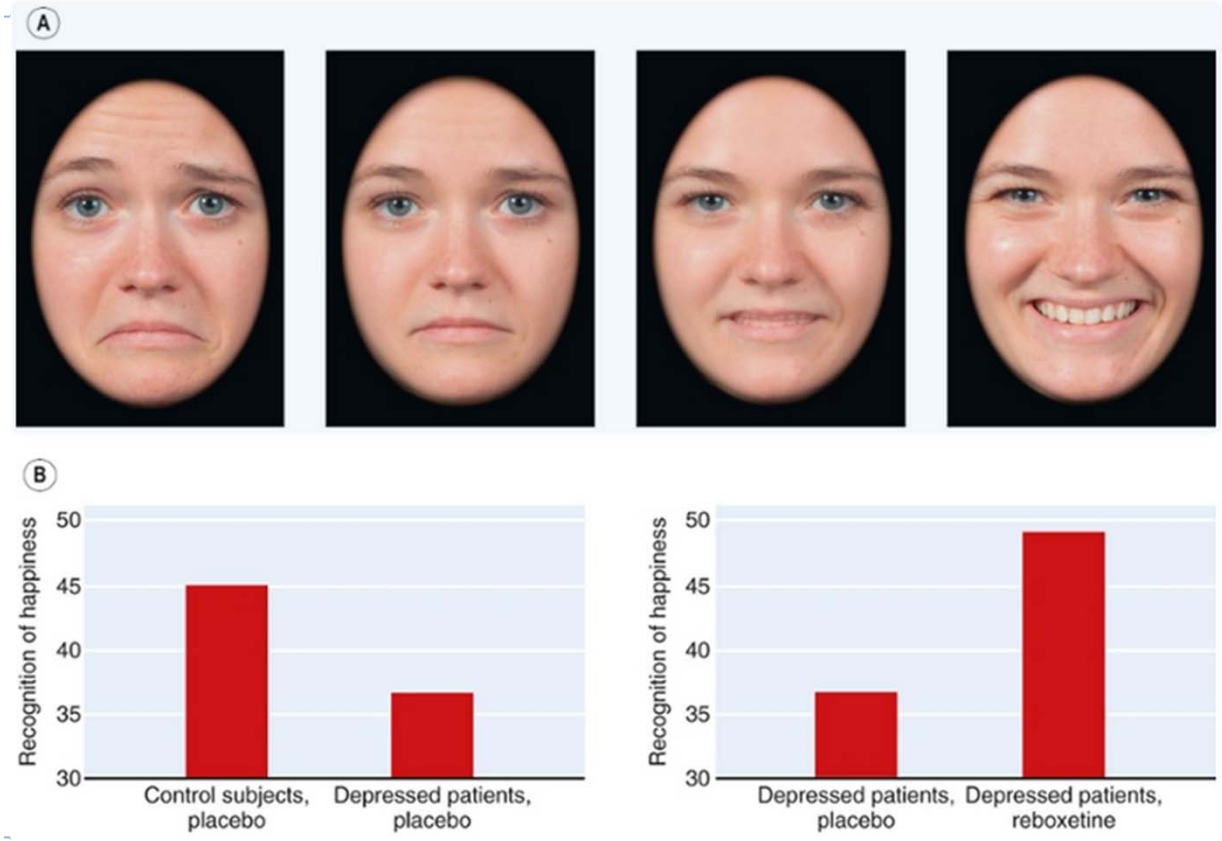
Symptoms of depression

- •Anhedonia- loss of interest in everyday activity
- •Despondent mood
- •Altered sleep patterns
- •Changes in weight/appetite
- •Persistent feelings of guilt
- •Morbid thoughts
- •Agitation
- •Inability to concentrate
- •Loss of executive memory
- •Indecisiveness
- •Negative affective bias

Physiological effects

- •Depleted monoamine neurotransmitters: **serotonin, norepinepherine, dopamine**
- •Degeneration of neurons and synaptic connectivity
- •Decreased GABA levels
- •Imbalanced HPT (hypothalamic-pituitary-thyroid) axis
- •Increased cytokine levels

Negative affective bias



Systems of diagnosis

DSM-IV

- Major depressive disorder: 2 weeks depressed mood or loss of interest accompanied by 4 additional symptoms
- Dysthymic disorder: 2 yrs depressed mood for more days than not

ICD-10

- Mild to moderate depression: common symptoms + functional impairment
- Severe depression: physical symptoms

Treatments available

- Antidepressant drugs (SSRIs, TCAs, MAOIs, 5-HT2 antagonists)
- Counseling (Cognitive therapy, interpersonal psychotherapy, non-directive counseling, befriending, exercise, problem solving therapy)
- Natural supplements (St Johns Wort)
- Electroconvulsive therapy (ECT)

Antidepressant drug classifications

- SSRIs (Selective Serotonin Reuptake Inhibitors)
  - fluoxetine (PROZAC)
  - citalopram (SEROPRAM)
  - paroxetine (PAROXAT)
  - sertraline (ZOLOFT)
  - escitalopram (CIPRALEX, SCIPPA)
  - fluvoxamine (FEVARIN)
- • SNRIs (Serotonin-Norepinephrine Reuptake Inhibitors)
  - – SSNRI (Selective Serotonin-Norepinephrine Reuptake Inhibitors)
    - venlafaxine (FAXIPROL, FALVEN) desvenlafaxine
    - duloxetine (CYMBALTA)
  - – TCA (Tricyclic antidepressants)
    - imipramine (MELIPRAMIN)
    - maprotiline (LUDIOMIL)
    - amitriptyline (TEPERINEP)
    - clomipramine (ANAFRANIL)

NRI (Norepinephrine reuptake inhibitors)

- reboxetine (EDRONAX)
- atomoxetine
- Bupropion (ELONTRIL, WELLBUTRIN SR)

Monoamine receptor antagonist (5-HT2, α2 antagonists)

- trazodone (TRITTICO AC)
- nefazodone
- mirtazapine (REMERON, MIRTADEPI)
- mianserin (MIAGEN)
- vortioxetine (BRINTELLIX)

Monoamine Oxidase Inhibitors

- selegiline
- moclobemide (AURORIX)

Melatonin receptor agonist

- agomelatine (VALDOXAN, LAMEGOM, ASSIMIL)

Tianeptine (COAXIL, TIALERA): Atypical μ-opioid receptor agonist, Serotonin reuptake enhancer, Glutamatergic, neurotrophic, and neuroplastic modulation, potentiates CNS D2 and D3 receptors

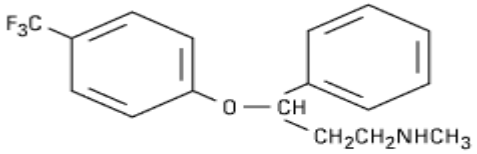
Selective Serotonin Reuptake Inhibitors

- **Similar efficacy with Tricyclic's, but lower side effects**
- **Introduced in the 1980s-90s**
- **Block serotonin uptake @ presynaptic 5-HT transporter**
- **Act on 4-TM ion channel receptors and 7-TM GCPRs**
- **Direct-to-consumer marketing**
- **Sales exceed $17 billion worldwide in 2003**
- **Interference with MDMA, cocaine, TCAs**
- **May initially increase suicide risk**

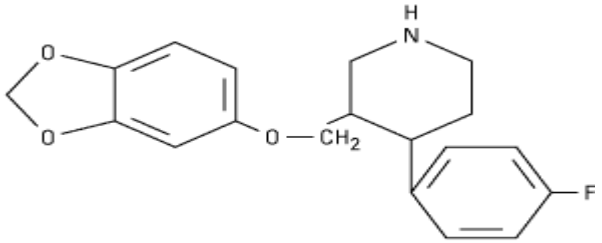
SSRIs (selective serotonin reuptake inhibitors)

- **citalopram** (Celapram, Chem mart Citalopram, Ciazil, Cipramil, GenRx Citalopram, Talam, Talohexal, Terry White Chemists Citalopram)
- **escitalopram** (Lexapro, Cipralex)
- **fluoxetine** (Auscap 20 mg Capsules, Chem mart Fluoxetine, Fluohexal, Fluoxebell, Fluoxetine-DP, GenRx Fluoxetine, Lovan, Prozac, Terry White Chemists Fluoxetine, Zactin)
- **fluvoxamine** (Faverin, Luvox, Movox, Voxam)
- **paroxetine** (Aropax, Chem mart Paroxetine, GenRx Paroxetine, Oxetine, Paxtine, Terry White Chemists Paroxetine)
- **sertraline** (Chem mart Sertraline, Concorz, Eleva, GenRx Sertraline, Sertraline-DP, Terry White Chemists Sertraline, Xydep, Zoloft)

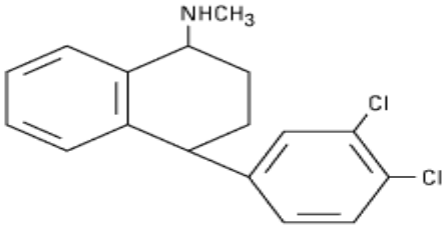
- • Adverse effects:
  - • seizures, convulsions
  - • sexual dysfunctions (effect on spinal neurons)
  - • QT prolongation (citalopram)
- • Clinical indication:
  - • MDD, sleep disorders
  - • OCD, bulimia
  - • GAD, panic attacks, social phobias



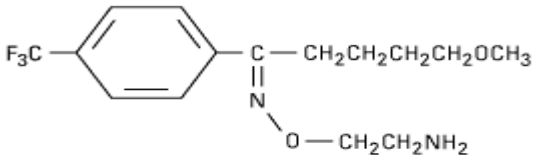
Fluoxetine



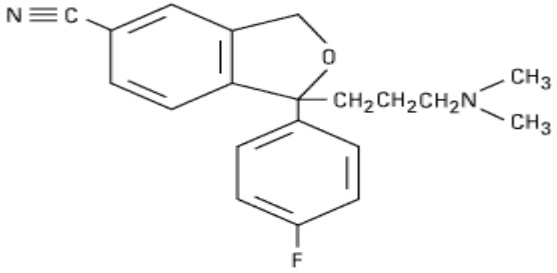
Paroxetine



Sertraline



Fluvoxamine



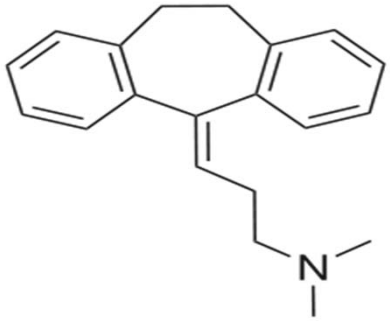
Citalopram

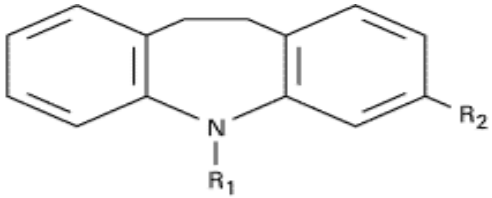
Pharmacokinetics of SSRI

- Fluoxetine--- Norfluoxetine (3xt1/2 than fluoxetine)
  - Should be discontinued before change to MAOI
  - Fluoxetine, Paroxetine CYP2D6 inhibitor!!! Inhibits of desipramine metabolism

Traditional Antidepressants

- **Tricyclic** antidepressants
  - **amitriptyline** (Endep, Tryptanol)
  - **clomipramine** (Anafranil, Chem mart Clomipramine, GenRx Clomipramine, Placil, Terry White Chemists Clomipramine)
  - **doxepin** (Deptran, Sinequan)
  - **dothiepin** (Dothep, Prothiaden)
  - **imipramine** (Tofranil)
  - **nortriptylline** (Allegron)
  - **trimipramine** (Surmontil)
- **Tetracyclic** antidepressants
  - **Mianserin** (Lumin, Tolvon)
- **MAOIs** (monoamine oxidase inhibitors) (non-selectives, irreversible)
  - **Phenelzine** (Nardil)
  - **Tranylcypromine** (Parnate): fast onset, short duration
  - **Iproniazid:** (several weeks)





R_1: $-(CH_2)_3N(CH_3)_2$
R_2: H

Imipramine

R_1: $-(CH_2)_3NHCH_3$
R_2: H

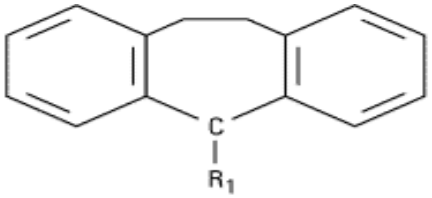
Desipramine

R_1: $-(CH_2)_3N(CH_3)_2$
R_2: $-Cl$

Clomipramine

R_1: $-CH_2CH(CH_3)CH_2N(CH_3)_2$
R_2: H

Trimipramine

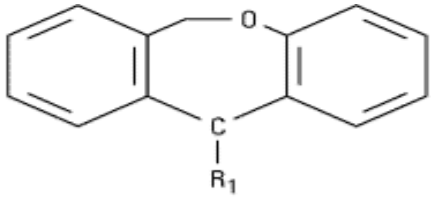


R_1: $=CH(CH_2)_2N(CH_3)_2$

Amitriptyline

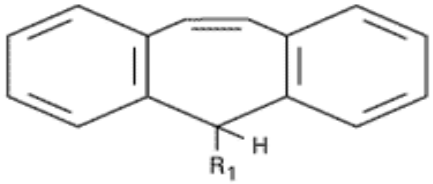
R_1: $=CH(CH_2)_2NHCH_3$

Nortriptyline



R_1: $=CH(CH_2)_2N(CH_3)_2$

Doxepin



R_1: $-(CH_2)_3NHCH_3$

Protriptyline

SNRI - TCAs

- MOA.:
  - • inhibition of SERT & NET
- • Adverse effects:
  - – anticholinergic effect
  - – orthostatic hypotension - α-blocking effect
  - – weight gain sedation – H1R blocking effect
  - – cardiac toxicity, QT prolongation
- • Clinical indication:
  - – MDD
  - – OCD (clomipramine)

Pharmacokinetics of TCA

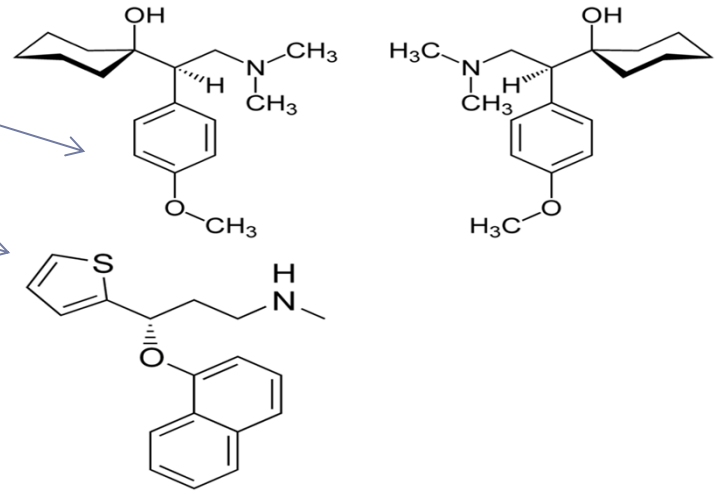
- Absorption is rapid
- Peak: 2-3 h
- Metabolism: extensive 1st pass
- Oxidation, hydroxylation, demethylation
- 5% = “slow acetylators”
- Protein bound: 90 – 95%
- Renally cleared

Cardiac Side-effects of tricyclic antidepressants

- Cardiac conduction delay
- Anti-arrhythmic at therapeutic doses
- Arrhythmigenic at toxic doses
- Minimal effects on cardiac output

SNRI – SSNRI (Serotonin-Norepinephrine Reuptake Inhibitors)

- MOA.:
- • selective inhibition of SERT & NET
  - – venlafaxine (Efexor-XR)
    - • weak inhibitor of NET
  - – duloxetine (Cymbalta)
    - • balanced inhibitor of SERT & NET
- • Adverse effects:
  - • narrow adverse effect profile (<TCAs)
  - • BP↑, HR↑ (venlafaxine)
- • Clinical indication:
- – MDD
- – pain syndromes (diabetic neuropathy, fibromyalgic pain)



Phamacokinetics of SSNRIs

- Venlafaxine ---- desvenlafaxine (CYP2D6)
- T1/2=11 h ---- 11 h
- 4-8 % unchanged (U) ---- 45 % unchanged (U)
- Lowest protein bounding: 27-30 %

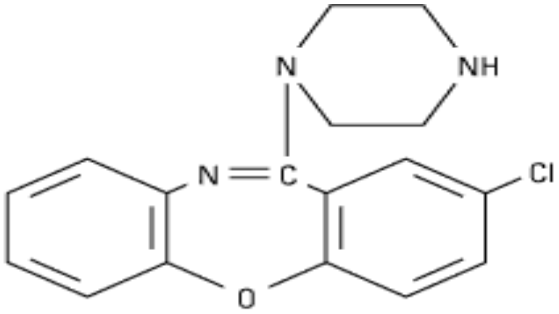
- Duloxetine – 97 % prot bound
- Metab: CYP2D6 and 1A2 (hepatic impairment prolongs)

5-HT2 antagonists

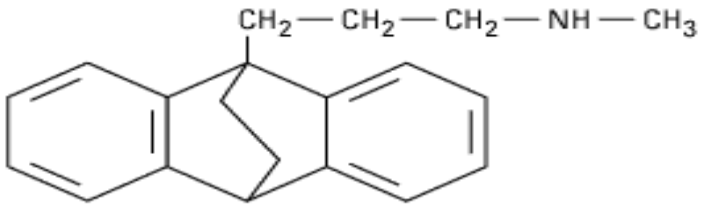
- MOA.:
  - antagonism on 5-HT2A receptors
    - – (lysergic acid, mescaline are agonists…)
  - inhibition of SERT & NET
    - – trazodone, nefazodone
      - antidepressant, antipsychotic, antianxiety effect
  - Adverse effects:
    - – sedation
    - – orthostatic hypotension – αR blocking
    - – GIT disturbances
  - Clinical indication:
    - sleeplessness (trazodone)

Pharmacokinetics of 5-HT2 antagonists

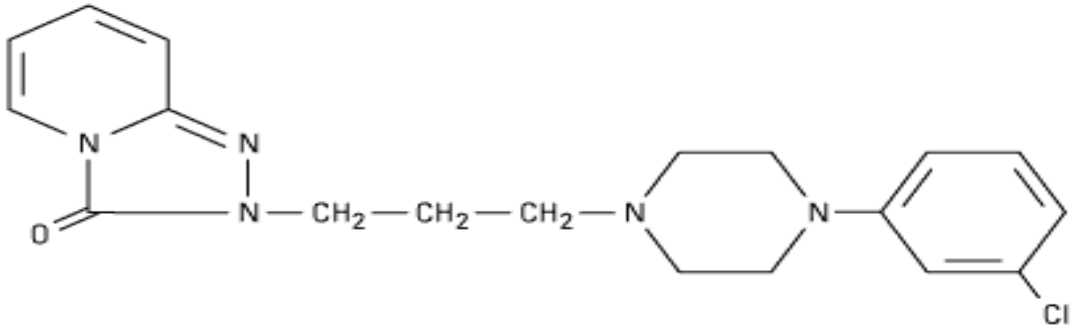
- Trazodone –nefazodone
  - Rapid absorption
  - Extensive hepatic metabolization
  - Highly protein bound
  - CYP3A4 inhibitor (nefazodone)



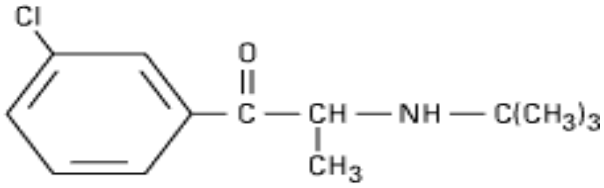
Amoxapine



Maprotiline



Trazodone

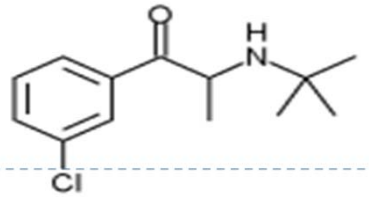


Bupropion

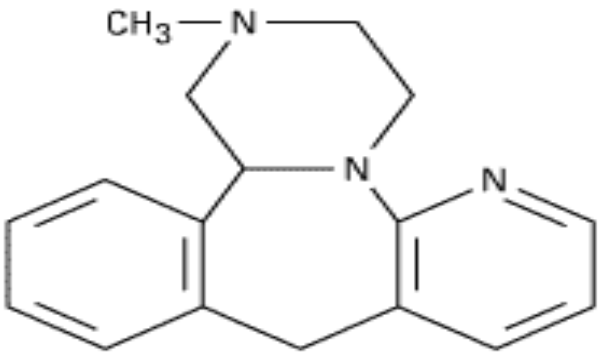
Tetracyclic and Unicyclic antidepressants

- • MOA.:
  - • modest inhibition of NET and dopamin reuptake
  - • antagonism on α2R, presynaptically
    - – bupropion, amoxapine, mirtazapine
- • Adverse effect
  - – sedation (mirtazapine – H1R blocking effect)
  - – pseudoparkinsonism (amoxapine – D2R blocking effect)
- • Clinical indication:
  - – smoking cessation
  - – reduce the symptoms of nicotin withdrawal

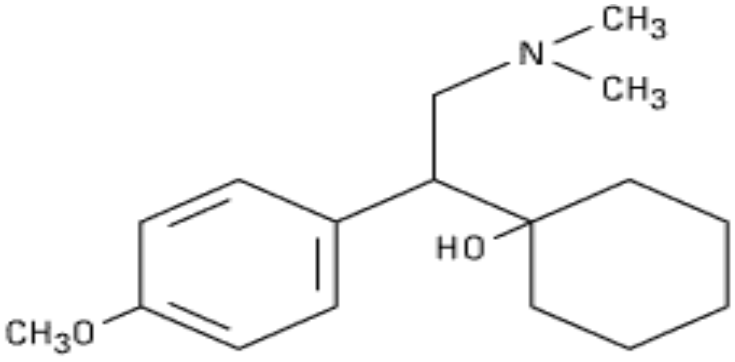
Bupropion



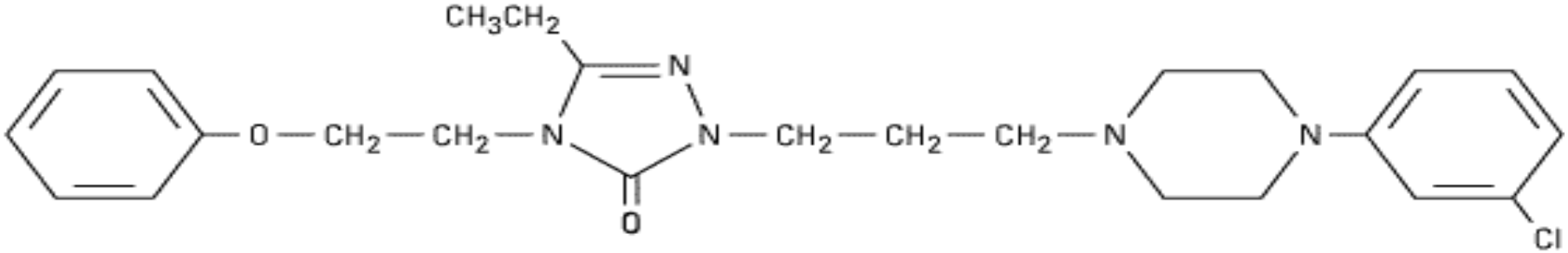
- blocks reuptake of norepinepherine and dopamine
- less risk of side effects
- used as an aide to quit smoking
- 85 % protein bound
- 3 active metabolite
- Biphasic elimination (1h, 14h)



Mirtazapine



Venlafaxine



Nefazodone

MAOI

- – phenelzine (irreversible nonselective MAO inhibitor)
- – moclobemide (selective, reversible MAO-A inhibitor)
- – selegiline (selective, irreversible MAO-B inhibitor)
- • Adverse effects:
  - • abrupt cessation – hypotonia, orthostatic collapse
  - • with SSRI – „serotonin syndrome”
  - • with tyramine – „cheese reaction”
- • Clinical indication:
  - • MDD
  - • anxiety, phobias
  - • parkinsonism (selegiline)

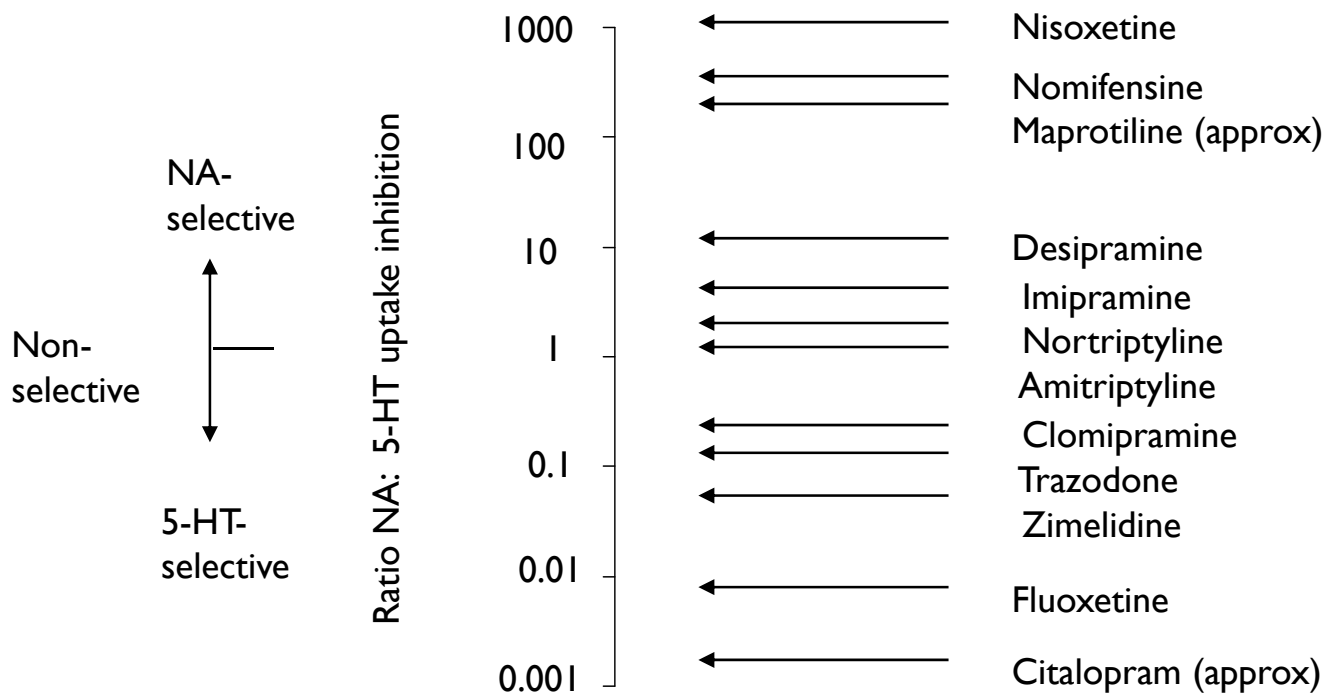
Newer antidepressants

- **RIMA** (reversible inhibitor of monoamine oxidase A)
  - **moclobemide** (Arima, Aurorix, Chem mart Moclobemide, Clobemix, GenRx Moclobemide, Maosig, Mohexal 150 mg, Terry White Chemists Moclobemide)
  - brofaramine
  - befloxatone
  - toloxatone

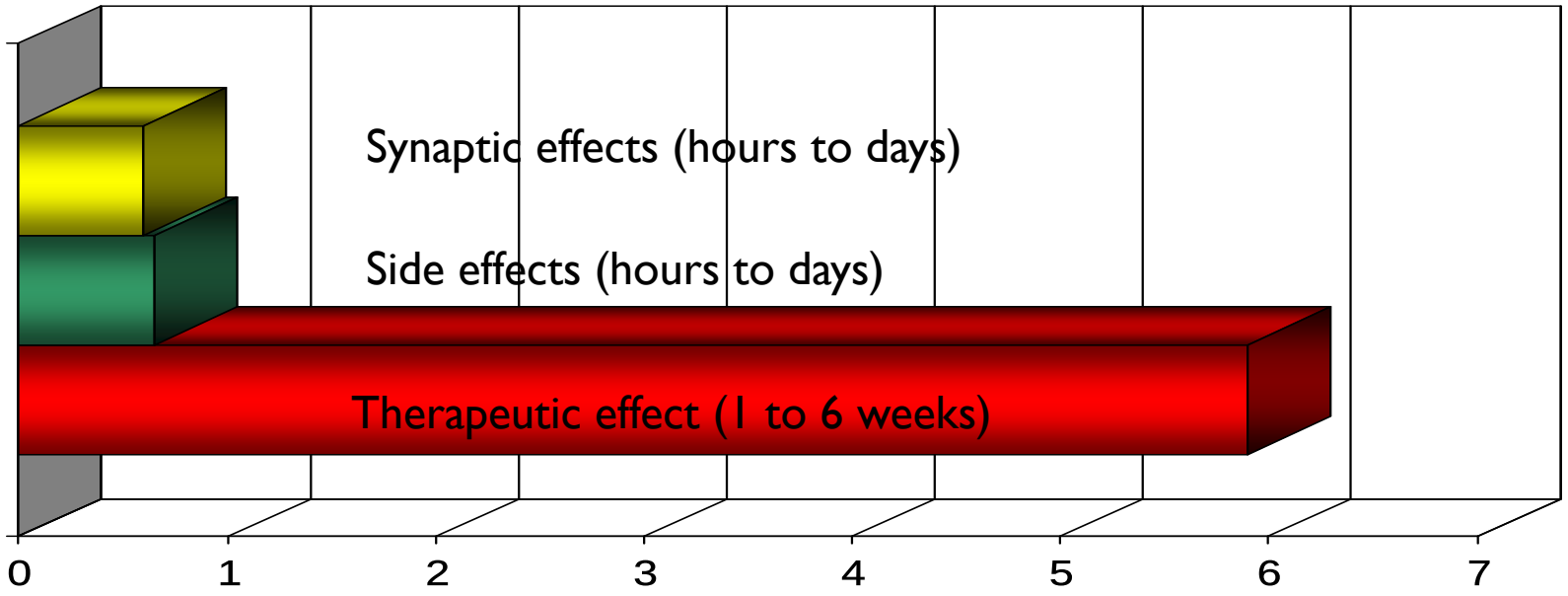
Newest antidepressants

- **NaRI** (selective noradrenaline reuptake inhibitor)
  - **reboxetine** (Edronax) most effective at improving social functioning, Side effects: blurred vision, hypotension tremors, headache, urinary hesitancy

Selectivity of antidepressants



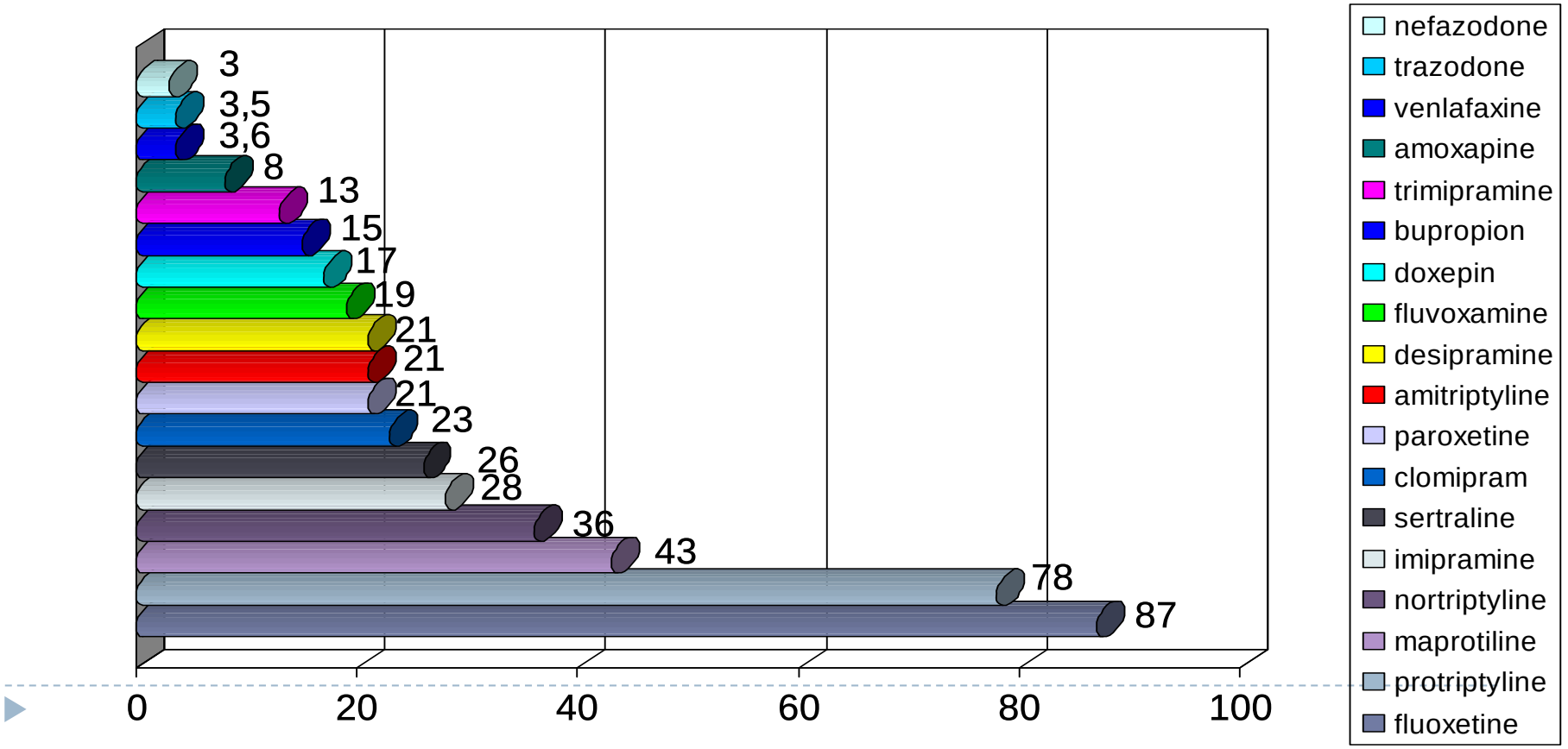
After Dosing Antidepressants (days)



Theories for 2-3 week delay in effectiveness

- Quickly increase serotonin concentration, which inhibits 5-HT firing, autoreceptors become desensitized after prolonged SSRI exposure
- Feedback regulation at 5-HT receptors requiring chronic administration to sustain therapeutic serotonin levels
- Need for alterations in genetic alpha and beta-adrenergic receptor expression
- Changes in nerve connectivity and neurotrophic factors

Antidepressant half-lives (hrs)



Antidepressant effects on several receptors and transporters

Antidepressant	ACh M	α_1	H_1	5-HT_2	NET	SERT
Amitriptyline	+++	+++	++	0/+	+	++
Amoxapine	+	++	+	+++	++	+
Bupropion	0	0	0	0	0/+	0
Citalopram, escitalopram	0	0	0		0	+++
Clomipramine	+	++	+	+	+	+++
Desipramine	+	+	+	0/+	+++	+
Doxepin	++	+++	+++	0/+	+	+
Fluoxetine	0	0	0	0/+	0	+++
Fluvoxamine	0	0	0	0	0	+++
Imipramine	++	+	+	0/+	+	++
Maprotiline	+	+	++	0/+	++	0
Mirtazapine	0	0	+++	+	+	0
Nefazodone	0	+	0	++	0/+	+
Nortriptyline	+	+	+	+	++	+
Paroxetine	+	0	0	0	+	+++
Protriptyline	+++	+	+	+	+++	+
Sertraline	0	0	0	0	0	+++
Trazodone	0	++	0/+	++	0	+
Trimipramine	++	++	+++	0/+	0	0
Venlafaxine	0	0	0	0	+	++

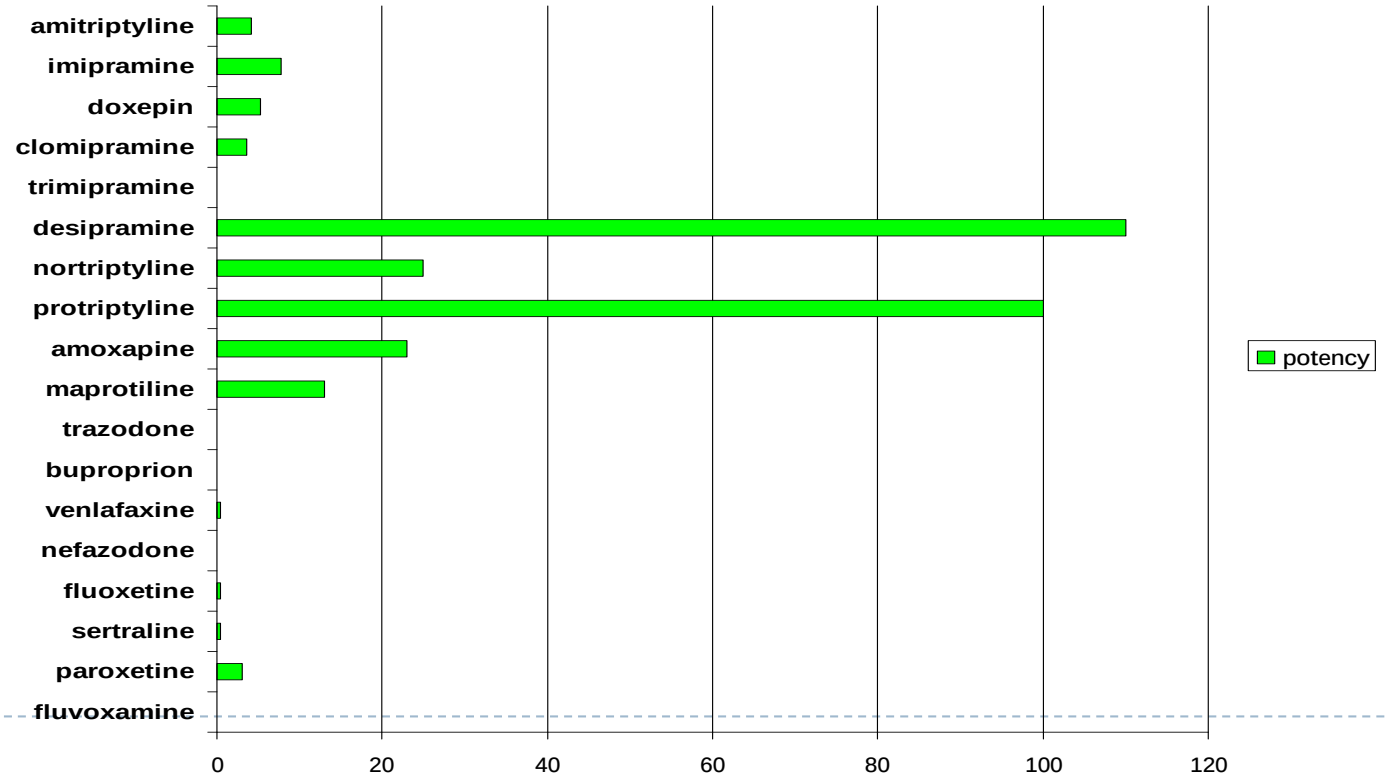
ACh M, acetylcholine muscarinic receptor; α_1, alpha$_1$-adrenoceptor; H_1, histamine$_1$ receptor; 5-HT_2, serotonin 5-HT_2 receptor; NET, norepinephrine transporter; SERT, serotonin transporter.

0/+, minimal affinity; +, mild affinity; ++, moderate affinity; +++, high affinity.

Norepinephrine uptake blockade
Possible clinical consequences

- Tremors
- Tachycardia

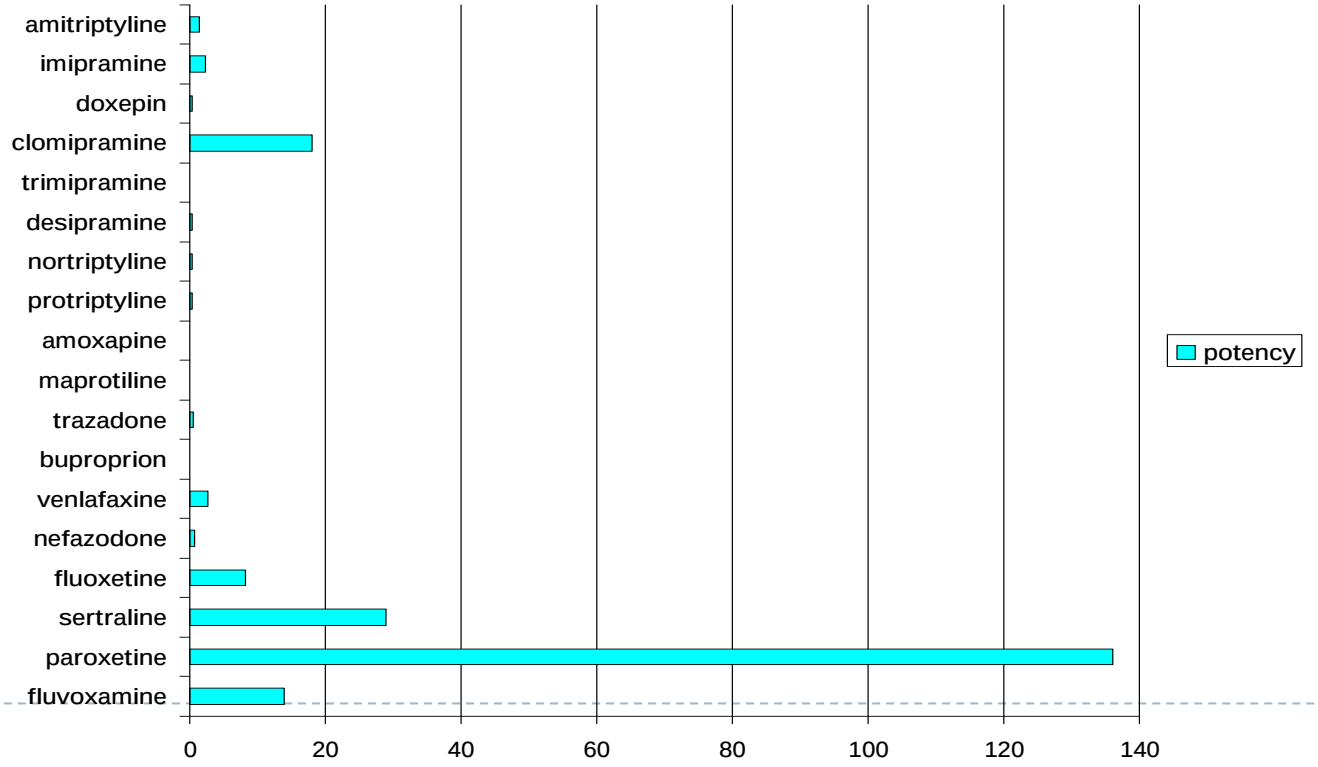
Norepinephrine uptake blockade (potency)



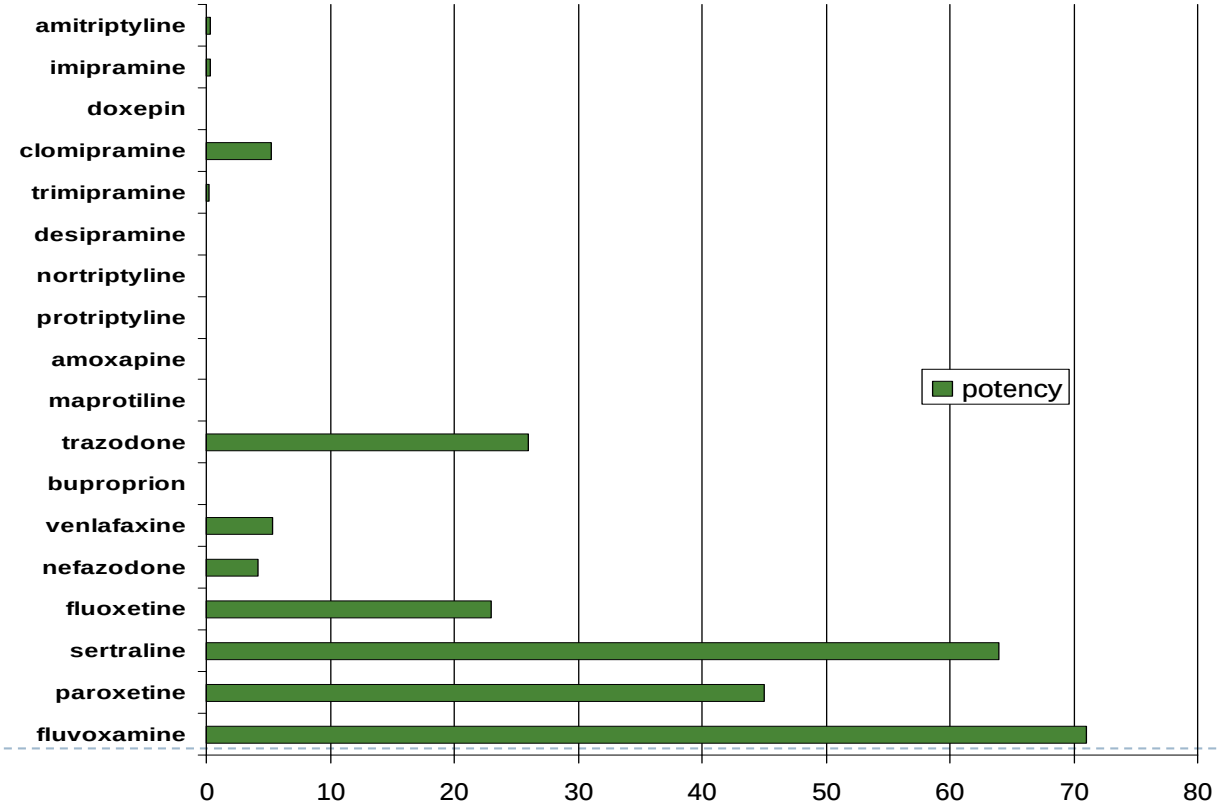
Serotonin reuptake blockade
Possible clinical consequences

- Gastrointestinal disturbances
- Anxiety (dose – dependent)
- Sexual dysfunction

Serotonin uptake blockade (potency)



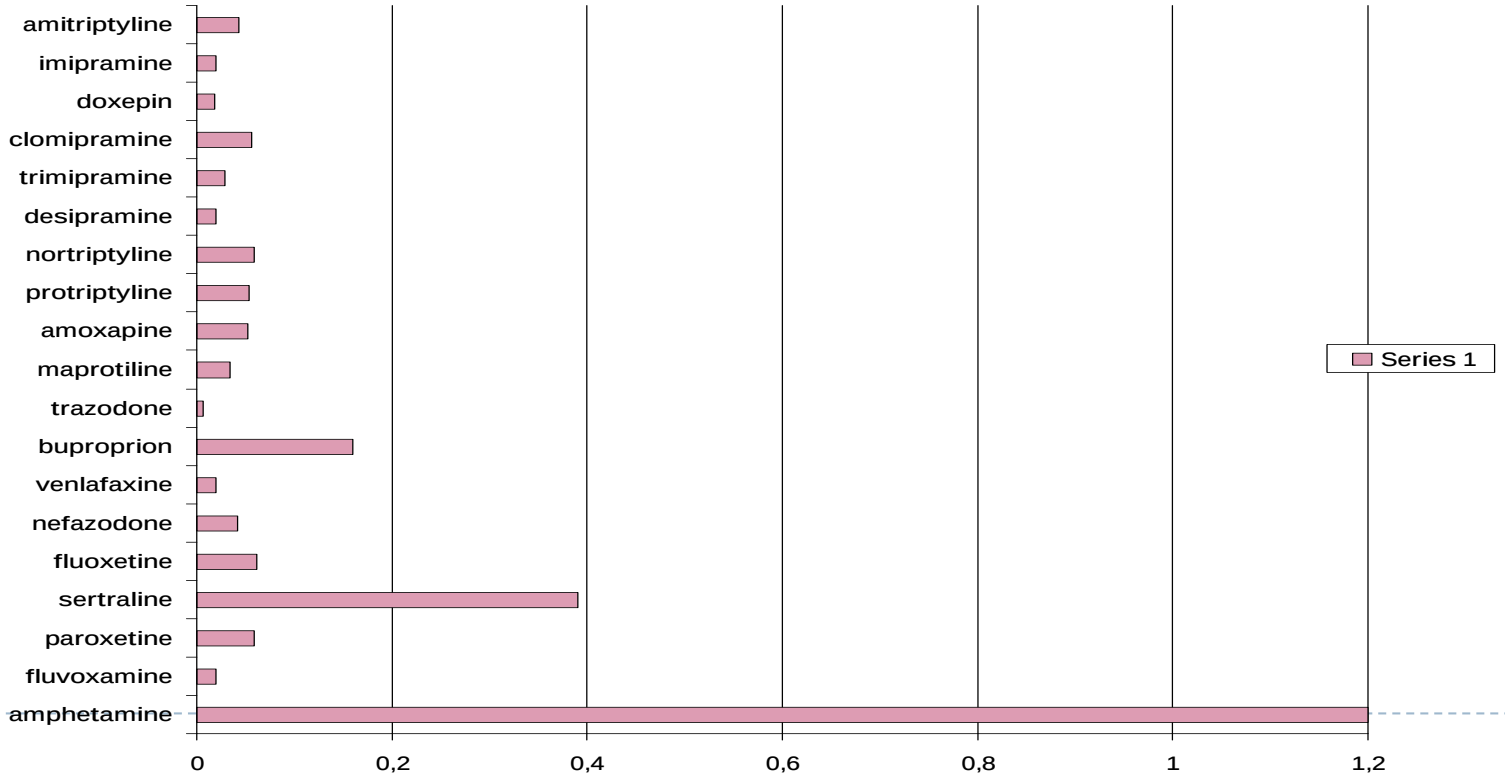
Blocking selectivity
5-HT vs. NE



Dopaminergic uptake blockade
Possible clinical consequences

- Psychomotor activation
- Antiparkinsonian effects
- Psychoses
- Increased attention/concentration

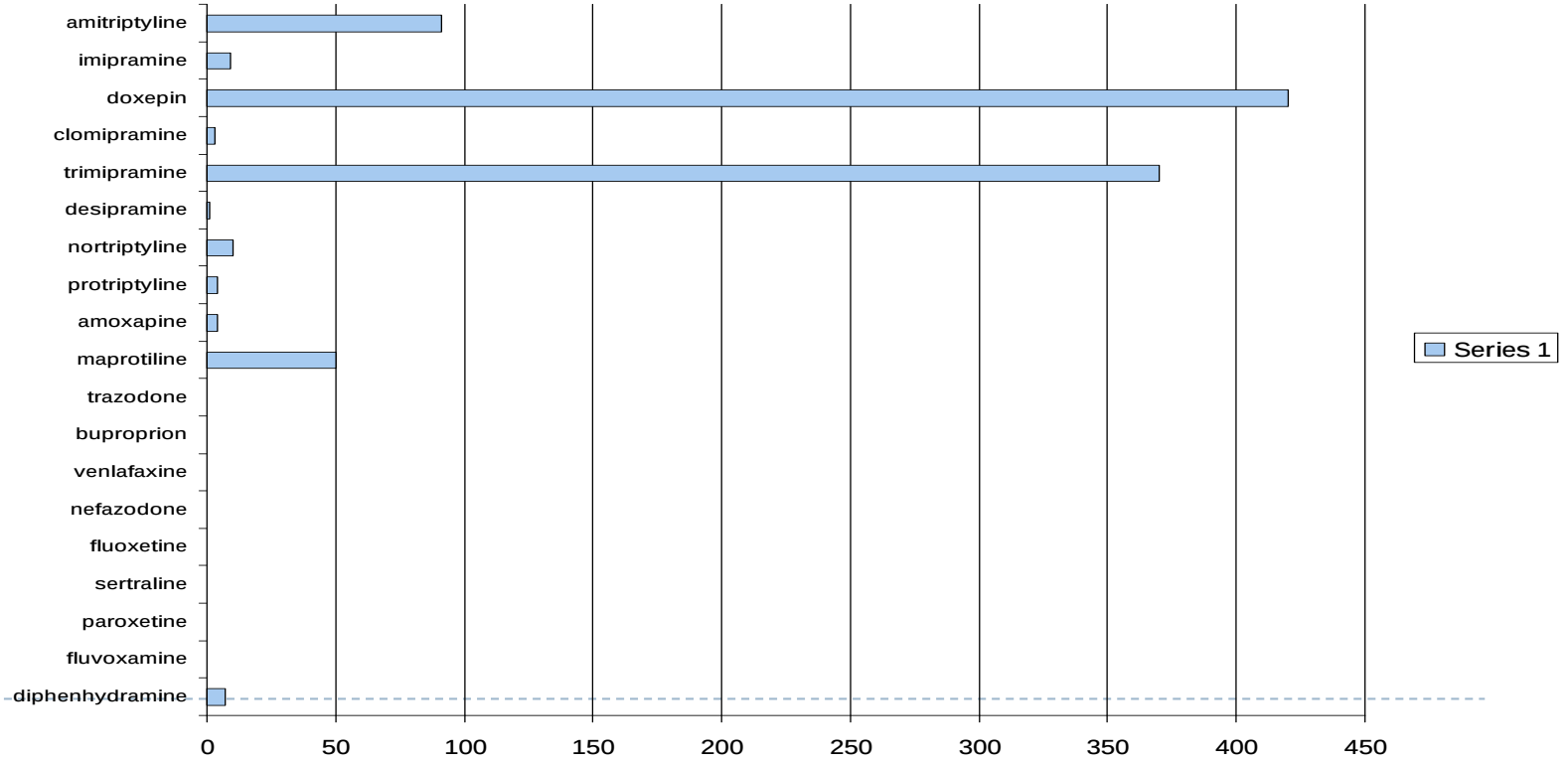
Dopamine uptake blockade (potency)



Histamine H_1 blockade
Possible clinical consequences

- Sedation, drowsiness
  - Weight gain
  - hypotension

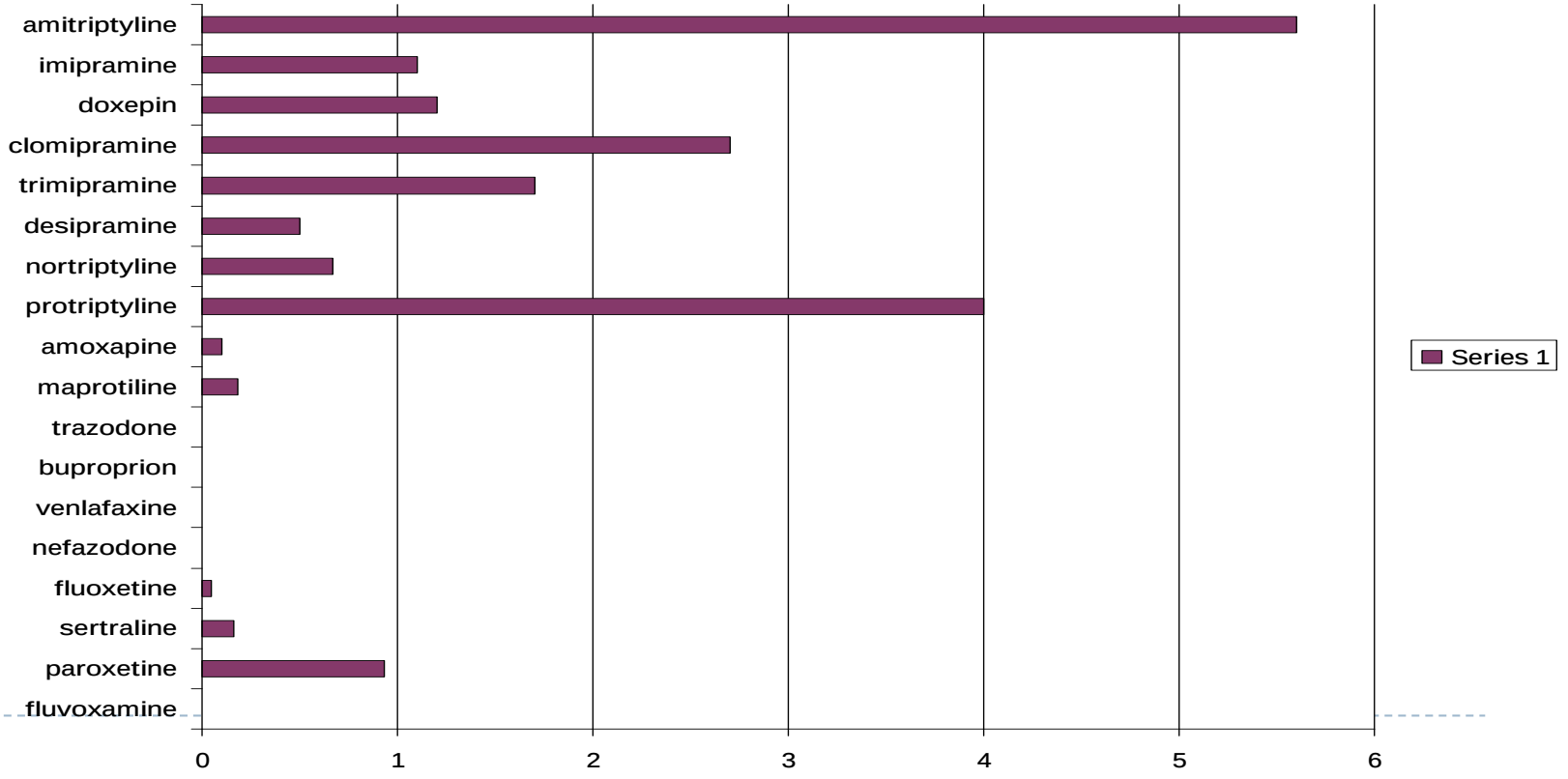
Histamine H_1 receptor blockade (affinity)



Muscarinic receptor blockade possible clinical consequences

- Blurred vision
- Dry mouth
- Sinus tachycardia
- Constipation
- Urinary retention
- Memory dysfunction

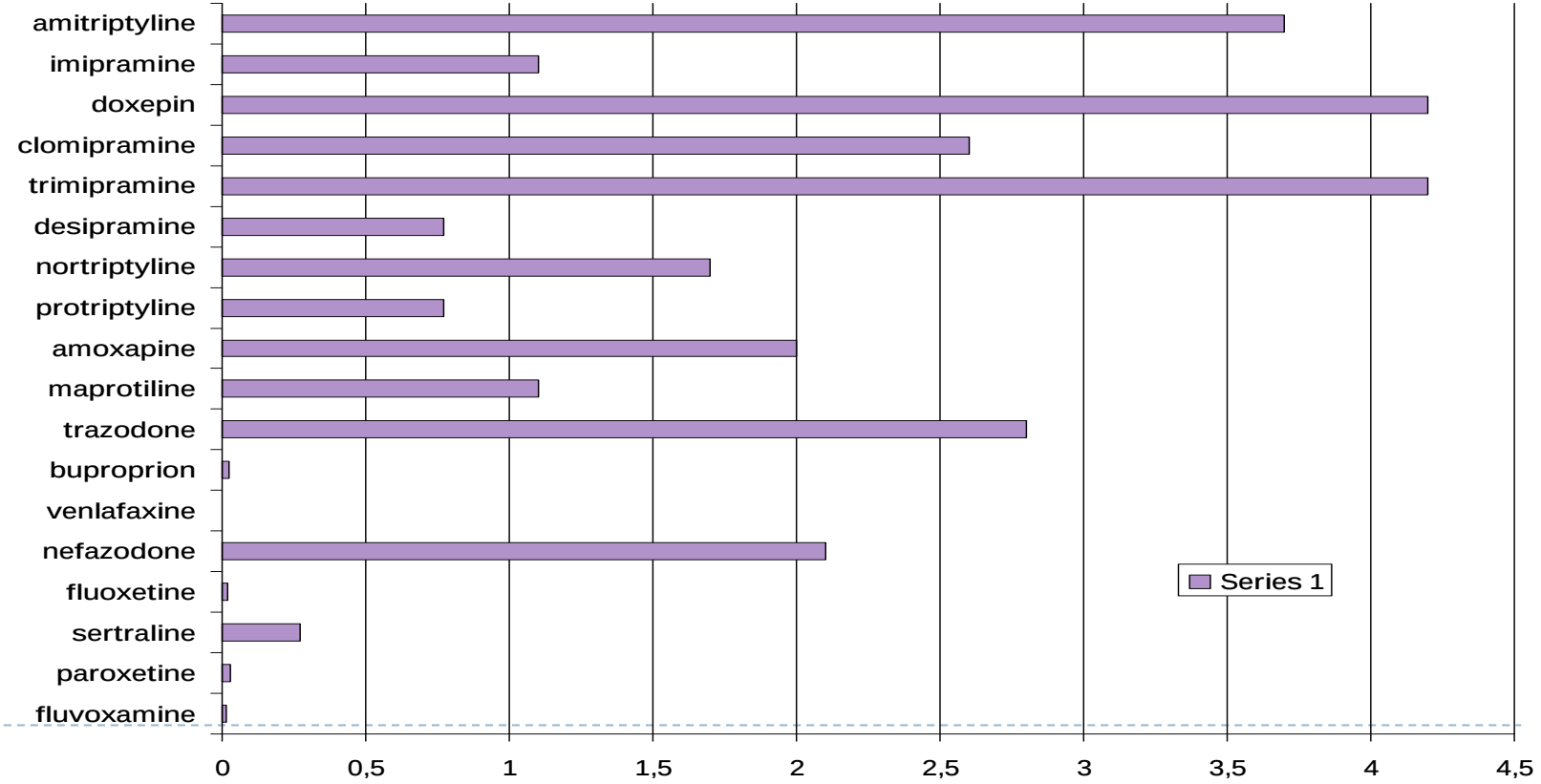
Muscarinic receptor blockade (affinity)



alpha – 1 receptor blockade possible clinical consequences

- Postural hypotension
- Reflex tachycardia
- Dizziness

alpha-1 receptor blockade (affinity)



Antidepressant Dis-continuation Syndrome

- Occurs within 3 days of cessation, only occurs after taking antidepressants for at lease 6 weeks
- Also occurs when switching antidepressants or switching to generic "equivalent" (may be up to 20% different)
- Flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, hyperarousal
- Generally resolves itself after 2 weeks
- Misleadingly termed "withdraw," since antidepressant are not habit-forming

Interactions (CYP450)

Enzyme	Substrates	Inhibitors	Inducers
1A2	Tertiary amine tricyclic antidepressants (TCAs), duloxetine, theophylline, phenacetin, TCAs (demethylation), clozapine, diazepam, caffeine	Fluvoxamine, fluoxetine, moclobemide, ramelteon	Tobacco, omeprazole
2C19	TCAs, citalopram (partly), warfarin, tolbutamide, phenytoin, diazepam	Fluoxetine, fluvoxamine, sertraline, imipramine, ketoconozole, omeprazole	Rifampin
2D6	TCAs, benztropine, perphenazine, clozapine, haloperidol, codeine/oxycodone, risperidone, class Ic antiarrhythmics, β blockers, trazodone, paroxetine, maprotiline, amoxapine, duloxetine, mirtazapine (partly), venlafaxine, bupropion	Fluoxetine, paroxetine, duloxetine, hydroxybupropion, methadone, cimetidine, haloperidol, quinidine, ritonavir	Phenobarbital, rifampin
3A4	Citalopram, escitalopram, TCAs, glucocorticoids, androgens/estrogens, carbamazepine, erythromycin, Ca^{2+} channel blockers, protease inhibitors, sildenafil, alprazolam, triazolam, vincristine/vinblastine, tamoxifen, zolpidem	Fluvoxamine, nefazodone, sertraline, fluoxetine, cimetidine, fluconazole, erythromycin, protease inhibitors, ketoconazole, verapamil	Barbiturates, glucocorticoids, rifampin, modafinil, carbamazepine

Antidepressant dose ranges

Drug	Usual Therapeutic Dosage (mg/d)
SSRIs	
Citalopram	20–60
Escitalopram	10–30
Fluoxetine	20–60
Fluvoxamine	100–300
Paroxetine	20–60
Sertraline	50–200
SNRIs	
Venlafaxine	75–375
Desvenlafaxine	50–200
Duloxetine	40–120
Milnacipran	100–200
Tricyclics	
Amitriptyline	150–300
Clomipramine	100–250
Desipramine	150–300
Doxepin	150–300
Imipramine	150–300
Nortriptyline	50–150
Protriptyline	15–60
Trimipramine maleate	150–300
5-HT_2 antagonists	
Nefazodone	300–500
Trazodone	150–300
Tetracyclics and unicyclics	
Amoxapine	150–400
Bupropion	200–450
Maprotiline	150–225
Mirtazapine	15–45
MAOIs	
Isocarboxazid	30–60
Phenelzine	45–90
Selegiline	20–50
Tranylcypromine	30–60

MAOIs, monoamine oxidase inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.