Pharmacological Treatment of Depression and Posttraumatic Stress Disorders in Traumatized Patients

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September 2010, revised September 2012

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ACKNOWLEDGMENTS

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Psychotropic drugs represent one of the available strategies in the multimodal and integrated treatment programs for traumatic stress. Pharmacotherapy is a part of the strategies, but doesn't substitute psychological support or psychotherapeutic interventions.

The use of psychotropic drugs is justified according to the hypothesis that trauma, among other factors, is related to adrenergic hyperactivity, serotonin deficiency or to Kindling/sensitization phenomenon. Furthermore, neuroimaging studies on PTSD diagnosed patients have shown a selective atrophy of the hippocampus, possibly related a specific alterations in the hypothalamic-pituitary-adrenal cortex axis. Antidepressant drugs could modulate neurotransmitters' function and act throughout neurotrophic activity.

To ensure safety in prescribing psychotropic medications, the single most important principle for the treatment of patients from various cultural and ethnic backgrounds is that the patient needs a trusting relationship with the prescribing clinician.

The second principle in any treatment plan is to make a culturally valid psychiatric diagnosis. Unfortunately, in many culturally diverse societies, patients from different ethnic backgrounds often receive either no psychiatric diagnosis for their psychiatric symptoms, or are over-diagnosed.

Validated screening instruments, such as the Hopkins Symptom Checklist-25 (HSCL-25) and the Harvard Trauma Questionnaire (HTQ), can help you make culturally appropriate diagnoses of major depression and PTSD (see Primary Care Provider [PCP] Toolkit: Healing the Wounds of Mass Violence).

Once diagnosed, a traumatized patient (e.g. refugee, civilian survivor of terrorism, mass violence or natural catastrophes, asylum seeker) with major depression, it is important to make a decision if the patient has any accompanying psychiatric diagnoses. In many cases the patient will have PTSD and/or depression and/or an anxiety disorder and/or substance and alcohol abuse.

The following are simple steps for prescribing medications in culturally diverse populations who have experienced trauma: they adhere to the indications approved by American and European Regulatory Agencies (FDA, EMA). However it is important that each patient be individually considered in spite of the prescribing principles that apply to the general population.

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Steps in the Pharmacological Treatment

Step 1: Review all Psychiatric and Medical Diagnoses

In many cases, patients suffer PTSD and concomitant neurological, cardiovascular or other major medical pathology; common is also drug and/or alcohol abuse.

List all psychiatric and medical diagnoses. Make a pharmacological treatment plan for each psychiatric diagnosis with consideration for culture and ethnicity.

Be sure to obtain a family history of mental illness. Ask if any other family member was diagnosed and treated for psychiatric disorders. Ask what medications worked and which ones did not. In case of previous psychotropic drug treatment get information about significant adverse drug reaction. It makes sense to prescribe the same drug or a medication in the same class as the one that was effective with the relative. A family history of bipolar disorder should alert the PCP to the possibility of switch to mania while on antidepressants.

Psychiatric illness is often causing, contributing to, or interfering with the care of the patient's medical problems: the opposite is also true.

Step 2: Consider the Ethnicity of the Patient in the Choice and Dose of Psychiatric Medications

Research has demonstrated that a patient's ethnic background may influence his or her response to psychiatric medication. This field is called ethnopharmacology, or "the study of differences in response to drugs based on varied ethnicity (On-line Medical Dictionary, 2000).

Asians, Africans, Hispanics, and Caucasians may respond differently to equal dosages of psychotropic medications. It is important to know the pharmacokinetics of psychotropic drugs.

There are wide ethnic variations in drug metabolism due to genetic variations in the drug-metabolizing enzymes. The most important enzymes for drug metabolism are the cytochrome P450 (CYP) group, such as CYP1, CYP2 and CYP3. The liver contains an abundance of these enzymes and is well recognized as the primary source of drug metabolism. For the most part genetic variations are responsible for reductions in the activity of a number of enzymes resulting in higher amounts of medication in the blood potentially resulting in untoward side effects. Awareness of such factors should lead to more cautious prescribing practices.

In addition, non-genetic factors can contribute to the activity of liver enzymes such as diet, nicotine, alcohol, caffeine, drugs and other substances, resulting both in induction (e.g. tobacco, high-protein diet on CYP1A2) and in inhibition of CYP enzymes (e.g. common food ingredients such as flavinoids or grapefruit juice on CYP3A4).

Sociocultural considerations represent another important dimension affecting pharmacotherapeutic response. Cross-cultural issues regarding diagnosis, beliefs, and expectations about treatment and its outcome, compliance with prescribed medication, placebo effect and use of traditional treatments may all impact on drug responses in more potent ways than biological mechanisms. Negative perceptions about psychotropic medications are frequently

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associated with non-compliance and poor therapeutic response. Expectations exert an important role in the clinical effects of pharmacotherapy.

Due to the limited scope of this paper, we are not able to address every ethnicity the Primary Care Provider (PCP) may treat. For ethnic groups not described in this paper it is recommended that an Internet search be performed. A sample of helpful guidelines for commonly prescribed psychotropic medications for African-Americans, Asians, Hispanics and Caucasians are as follows (please refer to Hill 2002 for thorough list of references):

Africans:

- Have higher rates of misdiagnosis and over-medication
- Increased risks of side effects from tricyclic antidepressants (TCAs) requiring lower maintenance doses.
- Tend to have a poor response to fluoxetine (Flouxetine).
- Rapid response to benzodiazepines such as clonazepam and lorazepam.
- Higher occurrence of extra pyramidal side effects (EPS) and tardive dyskinesia (TD) probably due to the combination of slow metabolism and overmedication, that contribute to the mistrust of mental health services reported among Africans.

Asians:

- Respond to lower dose of antidepressants, typically requiring starting doses and maintenance dose at half of the standard dosage for all psychiatric medications.
- Folk remedies may or may not interfere with psychotropic medication.
- Slow metabolizers resulting in higher levels of tricyclics, (TCAs) requiring lower dose.

Hispanics:

- May respond to lower doses of psychotropic medications
- Commonly use folk remedies, which may or may not interfere with psychotropic medication.
- Frequently report anticholinergic side effects to TCAs requiring half the dose given to Caucasians.

Step 3: Consider the Patient's Medical Status

Prior to prescribing psychotropic medication, the patient needs to have a basic medical history and physical examination. Routine blood work, a urinalysis, and an ECG should be performed. The PCP should understand the possible impact of dose and side effects of these medications in relation to the following major medical considerations:

1. The presence of cardio-vascular disorders, serious heart disease including an abnormal ECG and hypertension, could influence medical choice.
2. The presence of certain medical disorders can determine the choice and generally reduction of dosage of medications (e.g., liver disease will affect antidepressant metabolism). This is generally true with seizure disorders and would influence the choice of medication. Liver of kidney disease is sometimes a factor due to the metabolizing of

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medications and again, it depends on the choice of medication. Diabetes, however, is not necessarily a factor. (Refer to medication tables).

3. Consider the patient's use of traditional healing practices such as herbs. Some traditional remedies may contain nicotine or alcohol. The use of tobacco will reduce the blood concentrations of an antidepressant. Alcohol will synergize with all antidepressants and potentiate sedative effect of anxiolitics.
4. Consider whether the patient is in active treatment with another medical or psychiatric provider. Get a list of names of all medications taken, including over the counter medications. Ask to see all medication bottles.

Step 4: Age Considerations

With any age, it is recommended to implement the use of antidepressant medications using lower doses and to increase the dosage slowly. With all patients prescribed psychotropic medications, ***"Start Low, Go Slow."***

The elderly need special consideration and typically require lower doses of antidepressants than younger adults. Increases in doses should also be carried out slowly. Anyone over the age of 55 or with a history of cardiac disease should have a recent ECG reviewed prior to initiating antidepressants.

If the patient is a child 18 years or younger, he or she should whenever possible, be referred to a child psychopharmacologist for prescribing and/or monitoring medications. In the absence of a specialist, a psychiatrist treating adults or knowledgeable pediatrician should be able to treat children. Due to recent data indicating the possibility of increased potential of suicidal thinking or behavior with SSRI, the prescriber must be very conservative in their use, needs to warn of this possibility and monitor all patients closely for risk of suicide.

Step 5: Choose a Medication That Will Work Best For the Patient

Depression

Selective Serotonin Reuptake Inhibitors (SSRIs) are a first choice because they are generally well tolerated and have a fairly quick onset of action. However, one must have patience when prescribing these medications and allow them to reveal their efficacy over time (two, three weeks). Choices among SSRIs include fluoxetine, escitalopram, citalopram, paroxetine, fluvoxamine or sertraline. Table I can help make this choice.

Tricyclic Antidepressants (TCAs) and other categories of Antidepressants can be considered as choice, especially when SSRIs don't work or when they are not sufficient in monotherapy. Carefully considering the lower tolerability and the numerous counter-indication of TCA, they are especially indicated for patients with severe depression.

Several newer antidepressants (Mirtazapine, Venlafaxine, Duloxetine, Bupropion) can be considered as valuable, but less documented in the literature, alternative to SSRI and TCA.

Acute Stress Disorder

Psychotropic drugs have not a primary indication in ASD. They are considered less effective than psychotherapic and psychosocial interventions: they can negatively interfere in the

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patient/doctor relationship (over-evaluation of the psychiatric aspects and under-evaluation of human aspects of the trauma). Therefore pharmacological treatment of Acute Stress Disorder is essentially symptomatic:

- Short half-life Benzodiazepines (Triazolam, Brotizolam, Lorazepam, Alprazolam) or non-benzodiazepine hypnotics (Zolpidem, Zopiclon) are indicated for sleep problems. Trazodone is less effective than in PTSD.
- Benzodiazepines can relieve avoidant and intrusive symptoms and reduce hypervigilance. BDZ, however, can interfere on resilience and cause abuse, addiction and withdrawal symptoms.
- B-blockers (Propanolol) or α2 agonists (Clonidine) can also be utilized to reduce hypervigilance and flashbacks.
- Low dose typical or atypical antipsychotics can be utilized to treat psychomotor agitation and brief psychotic reactions.
- There is no drug effective on dissociative symptoms.
- Antidepressants are not generally indicated, even considering their long latency of action.

Posttraumatic Stress Disorder

Antidepressants are a good first choice, especially some SSRIs (Sertaline and Paroxetine that are approved by regulatory agencies; as alternative can be prescribed Fluoxetine, Escitalopram and Venlafaxine. TCAs are also potentially indicated to treat PTSD, but there are only few studies about their use. Two recent reviews support the status of SSRIs as first line agent in the pharmacotherapy of PTSD, as well their value in long term treatment.

In treatment resistant PTSD or as symptomatic treatment, other medications can be utilized, even though they are not approved by regulatory agencies.

The most common approach to the disorder is to treat with psychotropic drugs specific symptoms of PTSD as follows:

- BDZ, Propanolol and Clonidine to reduce anxiety and hyper vigilance.
- Non-benzodiazepine hypnotics, Prazosin, non-SSRIs Antidepressants (Trazodone, Mirtazapine), Antipsychotics (Quetiapine, Levopromazone) can be used to treat sleep disturbances and nightmares. SSRIs can make sleep worse. Sertraline is less effective than Paroxetine in sleep disturbances.
- Mood stabilizers (Lithium, Carbamazepine, Valproate, Lamotrigine, Topiramate, Levetiracetam, and Tiagabine) can be effective to treat discontrol, impusitivity, emotional instability.
- Low-dose typical and atypical antipsychotics (Risperidon, Olanzapine, and Quetiapine) are used to treat psychotic symptoms, agitation and impulsivity.

Step 6: Prescribing and Dosing Recommendations for Antidepressants and Adjunct Psychotropic Medications

Medications do not heal the psychological wounds of the traumatic experience, although they may consistently relieve the symptoms. Medications can help with the acute symptoms and facilitate the use of non-pharmacological treatments.

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In the case of all psychotropic drugs, begin with a small initial dose of the medication. The basic rule in prescribing any psychotropic medication for any ethnic group is "Start Low, Go Slow." However, this rule of thumb is even more important to keep in mind when prescribing medication for ethnic groups other than Caucasians. It is recommended that you introduce the psychotropic medication very slowly, due to some of the following considerations: (1) the fear of medication, especially if drugs were given for torture; (2) the rapid emergence of side effects in culturally diverse patients; and (3) the major cultural barriers related to poor adherence.

Review with the patient the most common side effects, as noted in Step 7 (below). When the patient has been given a prescription and educated on possible common side effects, offer the patient a way to easily reach you to discuss concerns or questions during the start-up phase. See patient again in 2 weeks, especially if there are side effects present or if the patient has anxiety regarding possible future side effects.

With antidepressants, remind the patient of the possibility of developing tolerance to some severe side effects in 2-3 weeks. Some patients do develop a tolerance and some symptoms remain, however, they are more likely to experience side effects and eventually adjust to these symptoms.

Patients should be warned about the use of alcohol with any of the psychotropic medications as the combination can intensify the effects of alcohol and decrease the effectiveness of the medication. The combination can also cause drowsiness and dizziness. Reminder: Alcohol decreases the seizure threshold.

Women should inform their PCPs if they are pregnant or could become pregnant prior to initiation of an antidepressant. It is unknown whether harm to unborn babies is a possibility with these medications. The patient should speak with her PCP if considering breast-feeding. As far as we can determine, the only drugs commonly used in psychiatry with proven relationships to specific birth defects are lithium, most anticonvulsants, paroxetine and benzodiazepines. Beyond this, there is no clear evidence that any standard psychiatric drug does not (or does) cause birth defects. However, there is a general suspicion that any drug might be bad for the fetus: whenever possible, drug therapy should be avoided in such instances. Anyway, when pharmacological treatment can't be avoided, a choice must be made between treating the patient and avoiding medicating the fetus: among antidepressants, all SSRIs, except Paroxetine, are category C agents (FDA: risk cannot be ruled out because of insufficient evidence): Buproprion is a category B drug (FDA: no evidence of risk in humans but adequate human studies may not have been performed); Venlafaxine and all TCAs are category D drugs (positive evidence of risk in humans), as well as Valproate and Carbamazepine. Risperidone, Olanzapine and Quetiapine are category C.

As with any medications, remind patients to keep medications in their original container, tightly closed, and out of reach of children. Store medications at room temperature and away from excess heat and moisture, such as the bathroom. Throw away any medication that is outdated or no longer needed.

It must be stressed that, although patients from different ethnic groups may require lower doses for effectiveness, each patient is an individual with individual responses. The PCP must consider dosage by the patient's symptom response.

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Selective Serotonin Reuptake Inhibitor Antidepressants (SSRIs)

Table 1 offers therapeutic dosage ranges for SSRIs commonly prescribed for Caucasians, as well as dosing recommendations for other ethnic groups. Bear in mind that some ethnic groups may require a dose more than 50% lower than that suggested by the package insert. Most medications in Table 1 take 2-3 weeks for initial symptom reduction; most medications require 4-6 weeks to reach full effectiveness. Closely monitor the patient's symptom response as well as side effects and make changes accordingly. Side effects will be addressed later in this paper. Drug interactions can occur with SSRIs possibly resulting in elevations of drug concentrations and a reduction in drug clearance. Never combine an SSRI with a monoamine oxidase inhibitor (MAOI).

Table 1. SSRI antidepressants, proposed therapeutic dose range, and adjustments for different populations that require lower doses than suggested in the Physicians' Desk Reference (PDR) or medication inserts.

Medication (generic name)	Therapeutic Dose Range for Adult Caucasians (mg)	Recommended Therapeutic Dose Range for Other Ethnic Groups (mg)	Comments
Escitalopram	10-20; initially 10, may increase up to 20 after one week	5-10; initially 5 for four weeks, reevaluate and may increase up to 10. Liquid available for doses <5	Fewer reported sexual side effects; faster onset of action. Do not use with history of seizure, hepatic, or renal disease. At least 14 days must elapse between discontinuation of Lexapro and initiation of an MAOI
Citalopram	20 once daily initially morning or night, with or without food; wait 1 week before increasing dose; max: 60; 40 recommended	10-20 daily initially; reevaluate; increase in 1 or more weeks; mas: 20-40	Same as Lexapro
Paroxetine	25-62.5; initially 25 in the morning, adjust by 12.5/day at one week intervals; max. 62.5 in the morning	12.5-25; initially 12.5 in the morning for four weeks, adjust as needed in one week intervals; max. 25 in the morning	Excellent for anxious depression and PTSD; may cause night sweats, sexual problems, more severe with withdrawal symptoms
Sertraline	25-200 one day dosing, mornings or night, initially 50/day; may increase in one week intervals; max. 200	12.5-200; 12.5 for several weeks, slowly increase to 25; max. 200; one day dosing in the morning	Excellent choice for anxiety and PTSD; may achieve clinical dose at lower dose
Fluoxetine	10-80; initially 5-10 in the morning; increase needed after several weeks; may give >20 in divided doses morning and noon; max. 80/day	10-40; initially 10 for two-four weeks, then may increase to 20; max. 40	Longer onset of action; safer to discontinue abruptly due to long half-life; not as effective with African-Americans. May cause insomnia, drowsiness, anxiety, anorexia, night sweats, nervousness
Fluvoxamine	100-300; initially 50-100 once daily, night, with or without food; >150 twice daily or more. Max 300/day	50-150; initially 50-100, max 150	Also effective in OCD; may contribute to sedation and fatigue in some patients through its sigma1 antagonism

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Tricyclic Antidepressants (TCAs)

TCAs may be a good choice but tend to have more side effects than the SSRIs. They are frequently prescribed when patients are unable to tolerate medications in the SSRI family. In some countries, SSRIs are not available, are not commonly used, or are not cost effective, making TCAs the natural choice. Table 2. offers therapeutic dosage ranges for TCAs commonly prescribed for Caucasians, as well as dosing recommendations for other ethnic groups. Keep in mind that some ethnic groups may require a dose more than 50% below the recommended dose on the package insert. Most TCAs in Table 2. take 2-3 weeks for initial symptom reduction and most require 4-6 weeks to reach full effectiveness. Closely monitor the patient's symptom response as well as side effects and make changes accordingly. Side effects will be addressed later in this paper.

Table 2. TCA antidepressants, proposed therapeutic dose range and adjustments for different populations that require lower doses than suggested in the Physicians' Desk Reference (PDR) or medication inserts.

Medication (generic name)	Therapeutic Dose Range for Adult Caucasians (mg)	Recommended Therapeutic Dose Range for Other Ethnic Groups (mg)	Comments
Nortriptyline	20-150 in 3-4 divided doses with or without food; initial dose 25 3-4 times/day	It is advisable to initiate treatment lower than 50/day in divided doses; increase by 10-25 per week as tolerated	Combining with an MAOI antidepressant can be fatal, good for patients with psychomotor retardation, not to be given in conjunction or within 14 days of treatment with an MAOI; good for chronic pain; PCP may want to perform blood test to help decide best dose; discontinue slowly
Imipramine Amitryptiline	25-300 in divided doses; initially 25 3-4 times/day; gradually increase as required and tolerated up to 150/day in divided doses; max. usually 200, if no significant response after three weeks, may increase up to 250-300/day	Start at 30-40/day in divided doses and increase dosages as tolerated by 25/week; max. 100 or as required and tolerated	Effectiveness may decrease over time; not to be given in conjunction or within 14 days of treatment with MAOI; contraindicated with existing severe hepatic or renal damage or history of blood dyscrasias, convulsive disorders, cardiac disease, glaucoma, patients taking thyroid medications; not to be administered to women of childbearing age, particularly during first trimester and last 7 weeks of pregnancy, or while breastfeeding; delayed response initially up to a few weeks; monitor for weight gain
Norpramine Desipramine	100 in single or divided doses; max. 300	25-100 in single divided doses; max. 150	Good for patients with psychomotor retardation, dosage should be initiated slowly at a lower level and increased according to tolerance and clinical response; discontinue slowly; may require plasma levels for dosing

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Other Categories of Antidepressant Medications and Adjunctive Agents

In the treatment of depression, several other medications are available either as single treatment choices or adjunctive agents to one of the SSRIs or TCAs for specific target symptoms. There are other classes of psychotropic medications useful in the treatment of depression when other psychiatric conditions exist, complicating the clinical picture of the patient. These medications are prescribed in adjunct with the primary antidepressant. Again, keep in mind that some ethnic groups usually require a lower dose of medication for effectiveness.

Table 3. Other classifications of antidepressants and adjunctive agents.

Medication (generic name)	Classification	Therapeutic Dose Range for Adult Caucasians (mg)	Recommended Therapeutic Dose Range for Other Ethnic Groups (mg)	Comments
Bupropion SR	Unicyclic antidepressant	When used primarily for depression: 150-300; initially 75-150 in the morning for at least one week ; increase to 150 BID with at least 8 hours apart; after several weeks may increase to max. 200 BID	When used for depression: 25-150; initially 100 in the morning for two weeks, increase to 100 BID; max. 150 BID When used as an "add-on" for sexual side effects: 25-50 initially and increase slowly on an individual basis and as indicated	Specific for drug, alcohol, and nicotine craving; may be effective for sexual side effects from SSRIs; energizing; contraindicated with eating disorders and history of seizures. Not to be used with patients with history of head injuries. Patients with an alcohol problem should not begin Wellbutrin while decreasing alcohol intake. Both increase the risk of seizures. Not good for patients with anxiety disorder
Medication (generic name)	Classification	Therapeutic Dose Range for Adult Caucasians (mg)	Recommended Therapeutic Dose Range for Other Ethnic Groups (mg)	Comments
Mirtazapine	Tetracyclic agent	15-45; initially 15 at bedtime, increase at intervals of at least 1-2 weeks	7.5; initially 7.5 for 3-4 weeks; slowly up to 30 at bedtime	Excellent for sleep at lower doses only; may mitigate SSRI-induced sexual dysfunction; good for anxiety, irritability, hyperactivity; may benefit negative symptoms of schizophrenia and psychotic depression
Venlafaxine	Bicyclic antidepressant	37.5-375; initiate at 37.5 for one week, then 75 daily, then re-evaluate after three weeks; max. 375	Initially 37.5 daily for two weeks; increase to 75 once/day dosing either in the morning or evening; re-evaluate after 3 weeks; max. 225	Good for treatment resistant depression and comorbid anxiety; similar dosing for depression and anxiety; may cause hypertension mainly at higher doses; must monitor blood pressure
Duloxetine	Serotonin and norepinephrine reuptake inhibitor (SNRI) Antidepressant	60-120; initially 60 once daily with or without food. Max 120	60-120; initially 60	Also used to treat fibromyalgia and diabetic neuropathic pain

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Medication (generic name)	Classification	Therapeutic Dose Range for Adult Caucasians (mg)	Recommended Therapeutic Dose Range for Other Ethnic Groups (mg)	Comments
Trazodone	Serotonin-2 Antagonists/Reuptake Inhibitor (SARI) antidepressant	50-6001; usual dose 100-150 at bedtime when used as an adjunct for sleep	25-150; initially 12.5 at bedtime; monitor sleep response and increase accordingly	Boosts effectiveness of primary antidepressant and excellent for insomnia; take at bedtime for effectiveness; good for dysthymia in depressed phase of bipolar disorder
Agomelatine	5HT2C antagonist and MT1 and MT2 agonist Antidepressant Anxiolytic	25, up to 50		Also used to induce sleep without intense sedation
Clonazepam	Anxiolytic	Initially 0.25 BID; after three days increase to 1, then every three days increase by 0.125-0.25; max. 4 day	0.25-1; initially 0.25 every day-BID; increase up to 0.5 BID; last dose at bedtime for sleep	Panic disorders, anxiety, insomnia
Lorazepam	Anxiolytic	1-10/day; initially 2-3/day in divided doses with largest dose at bedtime	0.25-1; initially 0.25 at bedtime, increase to 0.5 BID	Anxiety insomnia; for insomnia, give just at bedtime; adjust gradually
Alprazolam	Anxiolytic	Initially 0.25-0.5 TID; max 8/day	0.25-7; initially 0.25 2-3 times/day increasing slowly by 0.25 until symptom relief	Anxiety, panic disorders; not used with history of glaucoma; short half-life; may be more addictive; risk of seizures with quick discontinuation
Carbamazepine	Anticonvulsant	400-1600; initially 200 twice daily, then each week increase by up to 200, in divided doses. Max 1600	1000-150; initially 1000	Anticonvulsant agent used to treat mania; also efficient in discontrol of impulsivity. Asians could have a genetic predisposition to develop SJS and TEN
Valproate	Anticonvulsant	1200-2000; initially 1000, then increase rapidly in divided doses. Max 3000	000-1500; initially 1000	Anticonvulsant agent, mood stabilizer. Also available in extended release
Risperidone	Atypical Antipsychotic	2-6; initially 1-2; increase each day by 1 mg/day orally until desired efficacy is reached. Max 16	1-5; initially 1-2, increasing each day	Possible side effects like typical antipsychotics, especially at high doses (EPS, increased PRL)
Olanzapine	Atypical antipsychotic	10-20; initially 5-10 once daily, increase by 5 once a week until desired efficacy is reached. Max 20	10-20. Initially 5-10, increase until max 20.	Very frequent induces weight gain and sedation. Greater metabolic side effects compared to other atypical AP
Quetiapine	Atypical antipsychotic	400-800; initially 25 twice a day, increased by 25-50 twice each day until desired efficacy is reached. Max 800	400-600; Max 600	At low doses it may be a sedative-hypnotic. Frequent sedative effect. May increase risk for diabetes and dyslipidemia

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Step 7: Monitor Dose and Side Effects of Psychotropic Drugs at Therapeutic Doses

Now that you have chosen a suitable medication for the psychiatric diagnosis you have identified, make a decision on how ethnicity, medical conditions, current medications, and age will affect your use of it. Drug-drug interactions should be reviewed in the literature prior to choosing a drug: for example, Carbamazepine may decrease drug levels by induction, especially if the other drug is metabolized primarily by CYP-450-3A4. Therefore psychotropics such as TCAs and triazolobenzodiazepines (Alprazolam, Triazolam) may need dosage adjustments when administered along with CBZ. Furthermore, CBZ administration with most antipsychotics results in decrease in plasma concentrations of the antipsychotic. Valproic acid is a moderate metabolism inhibitor: it can increase amitriptyline serum levels and increased combined TCA

SSRIs:

The most common side effects of SSRIs include gastrointestinal problems, such as nausea, vomiting and diarrhea. These are frequently transient and may resolve after a week or two. Dizziness, drowsiness, and headaches are fairly common, as are dry mouth, moderate weight gain, poor overall sleep quality and vivid dreams. Sexual side effects are one of the most common reasons for discontinuing medication. The more frequently reported sexual side effects include decreased libido, anorgasmia, impotence, and delayed ejaculation. The incidence of sexual side effects may be as high as 30-40%. The clinician must ask the patient about sexual side effects as it often goes unspoken. Should sexual side effects occur, a complete sexual history should be obtained and behavioral techniques be explored. Determine other possible reasons for this problem and rule out medical disorders and depression as the cause. One could reduce the current dose, switch medications, use adjunctive medications, or simply monitor, as these side effects may diminish over the first few months of treatment. The clinician and patient may wish to weigh the risks and benefits received by SSRI in order to make an informed decision.

Serotonin syndrome can be a serious and potentially fatal side effect of all SSRIs. The clinician should observe for mental status changes, restlessness and agitation, and tachycardia. Later stages include hyperthermia, tremors, diarrhea, nausea and cardiovascular collapse. Contributing factors that increase the risk of serotonin syndrome include a high dose of an SSRI, the concurrent use of MAOIs, St. John's Wort, or dextromethorphan.

TCAs:

The most common side effect of TCAs is severe drowsiness; they are therefore best taken at bedtime. Weight gain, dry mouth, blurred vision, and urinary retention are also frequently reported. It is recommended that a baseline ECG be obtained due to possible conduction abnormalities. ECGs should be repeated for maintenance therapy. An important reminder is that therapeutic dosage range for TCAs is based on Caucasian males. Slow metabolizers, such as the elderly, are at higher risk of attaining toxic levels of TCAs. This class of medication can be lethal in overdose. Concurrent use of an SSRI with a TCA may result in toxic blood levels of the TCA and a decrease in drug clearance. Furthermore, both TCAs and SSRIs can cause a not well-defined but frequent side effect called Early Jitteriness Syndrome, which is characterized by jitteriness, sleeplessness, irritability, increased energy and anxiety and restlessness. Management strategies for this syndrome are initial slow titration from low doses of antidepressant, augmentation with benzodiazepines and symptomatic treatment with antipsychotics or beta-blockers.

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Other Categories:

- Bubropion: the most common side effects are insomnia, dry mouth and tremor.
- SNRIs: (venlafaxine and Duloxetine): their side effects are similar to SSRIs, due to their serotonergic effects. Furthermore, they can also cause dose-dependent increase in blood pressure, insomnia, sedation.
- Trazadone: the most common side effects are nausea, dyspepsia, liver failure, orthostasis, dizziness, headaches, visual trails, sedation, restlessness, priapism.
- Mirtazapine: due to its action on H1 receptors it can cause intense sedative effects and weight gain. Its serotonergic and noradrenergic effects cause symptoms similar to SSRIs and SNRIs.
- Agomelatine: the most common side-effects are headache, GI upset and naso-pharyngitis. It has fewer sexual side effects and less daytime sedation than those of most serotonergic ADS.
- Benzodiazepines: the most common side effect is sedation. Other effects include dissiness, weakness, ataxia, anterograde amnesia, decreased motor performance, nausea and slight hypotension. They can cause tolerance and addiction
- Carbamazepine: its side effects are sedation, dizziness, fatigue, nausea, ataxia, dyspepsia, LFT increases, rash, SIADH, arrhythmia, thrombocytopenia, aplastic anemia, lowerlevels of T3-T4. In overdose it can cause nausea, vomiting, CNS depression and seizures.
- Valproate: its side-effects are sedation, tremor, ataxia, dyspepsia, LFT increases, weight gain, pancreatitis, rash, hair loss, thrombocytopenia. In overdose it can cause the same effects of Carbamazepine.
- Atypical antipsychotics: the most common side effects are all atypical of APs are weight gain, increased risk for diabetes and dyslipidemia, sexual side effects, sedation, motor side effects, that can have a different incidence for each of these drugs. Furthermore, each AP can have specific side effects.

Side Effect Interventions for all Antidepressants:

1. Drowsiness: May be temporary; advise caution when driving or using machinery; take at bedtime.
2. Agitated and energized feelings: May be temporary; monitor for mania; consider changing to another antidepressant or consider adding a benzodiazepine (see Table 3).
3. Headaches: Monitor; rule out other causes; consider changing to another antidepressant; consider adding an analgesic.
4. Tremors: May be temporary; monitor; consider checking blood level if taking a TCA; consider changing to another antidepressant.
5. Changes in sexual functioning: All SSRIs can cause sexual side effects. Be sensitive when discussing and addressing with women and men; add another medication such as Viagra or Wellbutrin which increase blood flow but do not act as aphrodisiacs. Buspar sometimes helps with decreased libido and delayed orgasm but may produce insomnia or produce a "wired" effect. Consider changing to another antidepressant that may have a lower risk of side effects such as Bupropion or Mirtazapine (see Table 3).
6. Dry mouth: Increase fluids, consider water vs. drinks high in sugar; suggest sugar-free lozenges, lemon drops, candy and gum.

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7. Constipation: Increase intake of fluids, fiber, grains, vegetables, and products such as Fiber-Con or Metamucil.
8. Vivid dreams: Supportive counseling unless patient is having nightmares which are a result of PTSD and not a result of the medication.
9. Dizziness: Get out of bed more slowly; do not drive or operate dangerous machinery.
10. Weight gain: If monitoring calorie intake and increased exercise are not successful, change to an antidepressant that does not have a weight gain as a side effect such as Well butrin. Patients needing to gain weight do well with antidepressants that have weight gain as a side effect such as SSRIs, TCAs, or Remeron. Monitor weight (see Table 3).
11. Excessive sweating: Supportive counseling; consider changing to another antidepressant.

Reassure the patient that most side effects, if they occur, are not life threatening. Educate patients as to what they can do to reduce the discomfort and keep an open communication. Develop treatment strategies with the patient.

Step 8: Monitor Target Symptoms

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It is very important during each visit to evaluate the major target symptoms you are treating. During the first 4 weeks of treatment, it is wise to monitor closely and offer supportive counseling as the patient adjusts to the medication. It is during this initial period that patients may discontinue medication due to adverse effects. Throughout the entire course of treatment it is important to monitor the target symptoms and record the findings in the patients' medical record, comparing findings during subsequent visits. We recommend repeating the depression screen (HSCL-25) after the initial 12 weeks of treatment. After 12 weeks, the depression score should be under the 1.75 threshold. However, some patients may show improvement in symptom severity while scoring greater than 1.75 on the HSCL-25. In these cases, the PCP should continue medication at a tolerable dose and review with the patient other contributing factors and life stressors. When evaluating treatment response and target symptoms, one must also consider factors such as safety, housing, finances, or family problems. Some patients severely psychologically damaged from trauma may have chronic depression, requiring extra attention in getting proper level of counseling and social support, as well as medication. Some patients may take several years to adequately respond to treatments.

For example, always ask the patient with depression or posttraumatic stress disorders about:

1. Sleep: Determine the specific sleep problem, such as the quality and amount of time sleeping, whether the problem is falling asleep or interrupted sleep, and the reasons – i.e. nightmares, need to use bathroom, a crying baby.
2. Nightmares: Determine the number per night and per week, how long it has been a problem, and the content of nightmares. Compare to previous self-reports.
3. Appetite: Monitor appetite and weight changes. If necessary change medication. It is not necessary to change from one classification to another unless one experiences 2 failed treatments within one class.
4. Energy level: The PCP may see change in energy level reflecting either improvement in neurovegetative symptoms or a medication-induced mania. It is sometimes helpful for the patient to rate their level of energy by using a daily 0-5 scale to help describe changes. Make changes accordingly (see Table 3).

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5. Suicidal ideation: Immediately refer to psychiatry, crisis center, or nearest emergency room for evaluation and disposition. Make sure the patient is safely transported.
6. Mood: Re-administer and review with HSCL-25 every 2-3 months. Observe target symptoms for depression such as sleep, interest level, concentration, appetite, energy level, suicidality, and libido. For therapeutic interventions, see Table 3.
7. Anxiety: Monitor somatic complaints such as rapid heart rate, shortness of breath, headaches, and level of social functioning. Reevaluate medication dosage and consider adding a benzodiazepine (see Table 3).
8. Hyper arousal: value if there is a state of increase psychological and physiological tension marked by such effects as reduced pain tolerance, anxiety, exaggeration of startle responses, insomnia, fatigue, and accentuation of personality traits. For therapeutic interventions, see Step V.
9. Dissociative symptoms: determine the presence of depersonalization and derealization, that are common both in acute and posttraumatic stress disorder. Unfortunately there is not drug effective on such symptoms.
10. Discontrol, impulsivity: they can be controlled with low-doses antipsychotics and mood stabilizers.
11. Numbing: pay attention to the presence of behaviors used to struggle it, such as dangerous-extreme experiences.
12. Psychotic symptoms, agitation: they can be controlled with low-doses typical or atypical antipsychotics.

It is helpful for patients to keep a daily diary of target symptoms using a 0-5 scale. It is also helpful to give patients a simple handout describing the medication, his or her dose, and special instructions (best if written in patient's own language). Write the instructions directly on the medication bottle in patient's language, offer pillbox for daily use, help fill pillbox during early weeks and have patient bring pillbox to all appointments for your review. Pharmacists can be helpful filling medication boxes for the patient.

If the medications are working, keep the patient on the same medication for at least 12 months. Give specific instructions regarding changing or discontinuing medications. Stress the importance of continuing the medication once the symptoms have been relieved. Remind the patient that symptom relief could take months to occur. It is important to discuss with the patient any concerns they may have regarding the medication. Reinforce to the patient the importance of open communication, reinforcing that the prescriber and the patient are working in partnership.

Step 9: Switching Medications

If the patient has not had an adequate response on an antidepressant after a 12-week trial, the clinician should consider switching medication. When choosing an alternative antidepressant, one must keep in mind the original diagnostic criteria and target symptoms such as sadness, anxiety, low energy level, and insomnia, as well as side effect profile and medical co-morbidity. Due to genetic variability, a patient may not respond t o a specific SSRI but may respond to another. Staying within this class of antidepressants allows the clinician to taper the previous medication and begin the new one much more quickly with less risk of withdrawal symptoms. Many find it possible to stop one SSRI immediately and begin a new one. However, medications with shorter half-lives, such as paroxetine (Paxil), need to be tapered more slowly.

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SSRIs tend to inhibit isoenzymes of the cytochrome P-450 system. Many drugs, including SSRIs and TCAs, are metabolized by the isoenzyme 2D6. Therefore, SSRIs will increase blood levels of TCAs. When considering a switch to a TCA the clinician must begin with a low dose and slowly increase while tapering the SSRI. Some clinicians prefer to stop the SSRI, allowing at least a 2-week "wash out" period prior to starting a new antidepressant. Medications with long half-lives, such as Prozac, require a 4-6 week washout. This is particularly crucial if using an MAOI. A washout period appears less important when moving from one SSRI to another. Other commonly used drugs which could be affected by concurrent use of an SSRI include, but are not limited to, Type 1-C antiarrythmics, phenytoin, carbamazepine, and some beta-blockers.

Step 10: Discontinuing Antidepressants Treatment

Discontinuing antidepressant treatment should be a mutually agreed upon decision with the clinician and patient. Patients must be advised at the start of treatment not to abruptly discontinue their medications or to allow their medications to run out. It is recommended that the patient's symptoms be adequately treated for one year before considering the discontinuation of treatment. Once this decision is made the medication should be tapered: among SSRIs there are some differences depending on their different half-life and their active metabolites: for example, Fluoxetine may be stopped abruptly without much risk of discontinuation symptoms due to its very long half-life. On the contrary, Paroxetine needs a slow withdrawal, due to the fact that it inhibits its own metabolism: many patients tolerate 10 mg dose reduction every week. In discontinuing or tapering TCAs, it is most prudent to do so at a maximum rate of 25-50 mg every two-three days. The patient should be monitored during tapering every 3-4 weeks. They should be seen again after 4-8 weeks of being off the antidepressant to monitor for relapse. Supportive therapy, such as individual or group therapy, may provide the patient with the opportunity to sustain their improved health and function. Should there be a recurrence of symptoms, the patient should be advised to begin another trial with an antidepressant. The second round of treatment may continue 2 years before discontinuation is considered. Patients should be aware of the recurring and chronic nature of mood disorders.

Conclusion

Safe and effective use of antidepressants and other psychotropics can be achieved in all ethnic groups. A basic understanding of the prescribing principles and the variances in drug metabolism in various ethnic groups will help guide the clinician in their choice and dose of medications. It is always wise to "start low and go slow" when using any of these medications. However, once it is determine that an individual is tolerating a medication, the clinician should be certain to achieve an optimal dose in order to achieve remission of symptoms. Finding a limited formulary with which the PCP is comfortable with will allow optimal treatment choice with fewer complications. Always review with the patient the possible risks, benefits, side effects, and alternatives to treatment. Frequent recheck visits during dosage titration is advisable.

Information concerning approved medications is updated continually. New medications are rapidly being developed and marketed. Therefore, it is important for PCPs to be kept informed of new prescribing information and treatment choices. This paper will need to be updated on a regular basis to ensure that patients are given the benefit of new developments and choices in psychopharmalogic agents.

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