Medical Advisory Panel for the
Pharmacy Benefits Management
Strategic Health Group

The Pharmacologic Management of Major Depression in the Primary Care Setting

Department of Veterans Affairs
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THE PHARMACOLOGIC MANAGEMENT OF MAJOR DEPRESSION IN THE PRIMARY CARE SETTING

This guideline is to be considered supportive of the VHA/DoD guideline and is specific to pharmacologic management issues

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The Medical Advisory Panel for the Pharmacy Benefits Management Strategic Healthcare Group

Mission

The mission of the Medical Advisory Panel (MAP) for Pharmacy Benefits Management (PBM) includes the development of evidence-based pharmacologic management guidelines for improving quality and providing best-value patient care.

The MAP comprises practicing VA and Department of Defense physicians from facilities across the nation:

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Strategic Healthcare Group (SHG)

VHA's PBM SHG has been directed by the Under Secretary for Health to coordinate the development of guidelines for the pharmacologic management of common diseases treated within the VA, establish a national level VA formulary, and to manage pharmaceutical costs, utilization, and measure outcomes as they apply to patient care. The MAP provides support and direction to the PBM staff, located in Hines, Illinois.

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Guideline Development Process

Summary
This evidence-based guideline on the management of patients with major depression is intended to update the August 1997 publication of the PBM-MAP The Pharmacologic Management of Major Depression. Whenever possible, the PBM and MAP relies upon evidence-based, multidisciplinary, nationally recognized consensus statements for the basis of VA guidelines. Relevant literature is reviewed and assessed with consideration given to the VA population.

Development Process and Sources of Information
Development of the guidelines relied upon the following consensus documents: *Depression Guideline Panel. Depression in Primary Care. Volume 2. Detection and Diagnosis. Clinical Practice Guideline, No 5. Rockville, MD. U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR Publication No. 93-0551. April 1993, The Texas Medication Algorithm Project: Report of the Texas consensus conference panel on medication treatment of major depressive disorder. J Clin Psychiatry 1999;60:142-56, American Psychiatric Association. Practice Guideline for Major Depressive Disorder in Adults. Am J Psychiatry 1993; 150(suppl 4): 1-26, Pharmacologic Treatment of Acute Major Depression and Dysthymia: Clinical Guideline, Part 1 and Part 2. Ann Intern Med 2000;132;738-756.*

The algorithm and annotations are in part based on the major depression guideline developed in 1997. To update this information, the literature following the publication of the 1997 document was searched (search queried articles published 1995 to 2000). A literature search of MEDLINE was conducted including the following search terms: major depression, serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, venlafaxine, nefazodone, mirtazapine, St. John's wort, drug interactions, side effect, clinical trial, review, meta-analysis. The literature was limited to adult human subjects and articles published in the English language. The bibliographies of articles and consensus documents were reviewed for additional relevant literature.

Methods to Formulate Recommendations
The literature was critically analyzed with evidence grading. The rating scale used for this document was based on the evidence rating used by U.S. Preventative Services Task Force (http://text.nlm.nih.gov/cps/www/cps.3.html), adapted from the Canadian Task Force on the Periodic Health Examination.

Strength of Recommendation
A: There is good evidence to support that the intervention be adopted.
B: There is fair evidence to support that the intervention be adopted.
C: There is insufficient evidence to recommend for or against the intervention, but recommendations may be made on other grounds.
D: There is fair evidence to support that the intervention be excluded.
E: There is good evidence to support that the intervention be excluded.

Quality of Evidence
I: Evidence obtained from at least one properly randomized controlled trial.
II-1: Evidence obtained from well-designed controlled trials without randomization.
II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
II-3: Evidence obtained from multiple time series studies with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III: Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.
Recommendations were based on evidence published in the medical literature. Where evidence was not available, expert opinion of the MAP was used. After review and discussion by the PBM-MAP, the draft guideline was sent to experts in the field of psychiatry for review. The draft document was then circulated to practicing clinicians (primarily psychiatrists and primary care providers) for clarity and applicability.

Use of the Guidelines
The guideline is divided into four sections: Executive Summary, Algorithm, Annotations, and Appendices. The algorithm is intended to provide a systematic approach to the management of patients with major depression. The letters within the boxes in the algorithm

refer to the corresponding annotation. The annotation is a further discussion of the evidence for making each recommendation. Details on drug therapy are provided to encourage the safe and effective implementation of the pharmacotherapy recommendations made in this guideline. Recommendations discussed in the annotation are referenced and graded according to the grading system outlined above. The appendices provide additional information for the clinician when considering treatment options.

The purpose of the guidelines is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. This guideline attempts to define principles of practice that should produce high quality patient care. They are attuned to the needs of a primary care practice but are directed to providers at all levels. The guidelines also serve as a basis for monitoring local, regional and national patterns of pharmacological care.

Guidelines should not be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the same results. The clinician in light of individual patient situations must make the ultimate judgment regarding the propriety of any course of conduct.

Plan for Implementation

The guideline will be available on the Pharmacy Benefit Management Strategic Health Group home page at http://vaww.pbm.va.med.gov or www.vapbm.org. It is recommended that a hard copy be kept on file in the medical libraries. Distribution to all clinicians who manage patients with major depression is strongly recommended. Clinicians are encouraged to have a copy of the document or a summary of key points available for reference when treating patients with major depression.

A summary of key points in a pocket card version will be developed by the PBM-MAP and made available.

Providing continuing education programs (e.g., medical grand rounds, on-line review of guideline) will be developed.

Departmental and individual education at the facility is also encouraged.

Updating the Guidelines

The PBM will review the guidelines routinely. Updating will occur as new information is made available from well-designed, scientifically valid studies and as outcome data may direct. Any member of the VA community is encouraged to recommend changes based on such evidence.

A current copy of the pharmacologic management guidelines can be obtained from Pharmacy Benefits Management home page at http://vaww.pbm.va.med.gov or www.vapbm.org.

Acknowledgments*

The MAP collaborates with physician members of the Veterans Health Administration Major Depressive Disorder Technical Advisory Group and VISN Formulary Committees in developing these guidelines. We gratefully acknowledge and thank those clinicians for sharing their expertise in this area.

Draft guidelines were disseminated for peer-review through the VISNs, prior to their completion. The PBM and the MAP would like to acknowledge and thank the following individuals who contributed both their time and effort to this process.

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* This list does not represent all the clinicians who reviewed the guideline, rather those who wished to be acknowledged. The Medical Advisory Panel and Pharmacy Benefits Management take full responsibility for the content of this guideline

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EXECUTIVE SUMMARY

1. Up to one in eight individuals may require treatment for depression during their lifetimes.

2. Given the high prevalence of depressive symptoms and major depressive episodes in patients of all ages, depression should be routinely considered and treated by primary care and other non-psychiatric practitioners.

3. The diagnosis of depression is based on assessment of the patient's mood, behavior, and physical symptoms. Some clinicians use structured interviews or questionnaires to assist in screening and/or diagnosis of depression. The choice of which particular screening instrument to use should be left to the discretion of the practitioner.

4. No one antidepressant medication is clearly more effective than another. No single medication results in remission for all patients. Patient specific factors and drug side effect profiles may favor one class of antidepressants over another, but there are no clear differences in efficacy among or within classes.

5. Selective Serotonin Reuptake Inhibitors (SSRIs) should be considered first line antidepressants for most patients in the primary care setting because of their low toxicity relative to other available antidepressants. There is insufficient evidence to recommend one specific SSRI over another.

6. Although there are many non-emergent conditions that warrant psychiatric referral, patients who present with depression and suicidal thoughts and/or symptoms of psychosis should receive an immediate evaluation by a psychiatrist.

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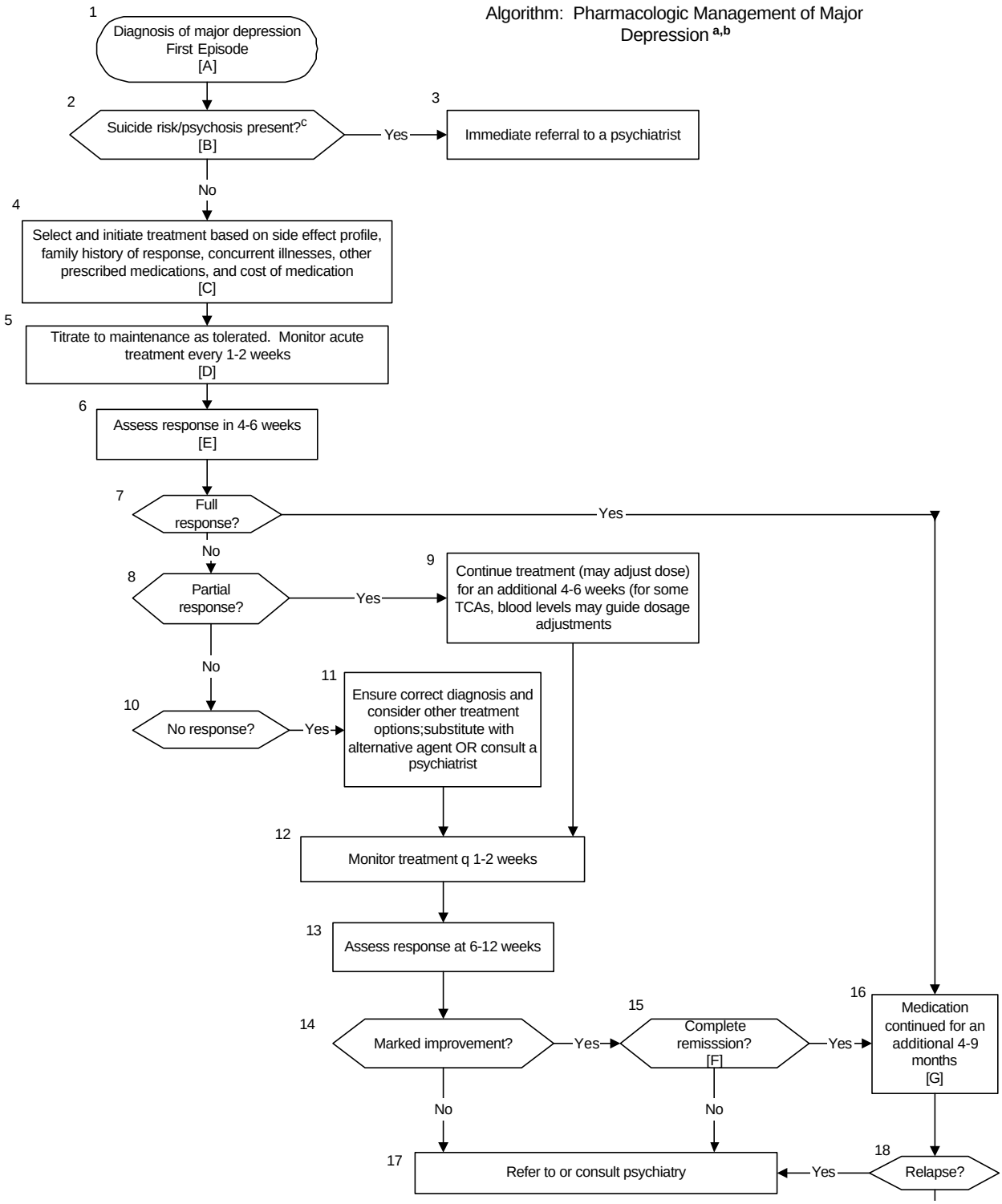
Algorithm: Pharmacologic Management of Major Depression [a,b]



[a] Adapted from Clinical Practice Guideline AHCPR

[b] Psychiatry referral may be requested at any point during the algorithm at providers' discretion. Once stable, patient should be referred back to their primary care physician.

[c] A psychiatric referral should be considered if any of the following is present:
psychotic features, assaultive behavior, and/or homicidal/suicidal thoughts, worsening of symptoms despite treatment treatment failure after 2 trials of medications in different drug classes, failure to respond to monotherapy or when higher than recommended doses are needed, behavioral toxicity, clinically significant seasonal pattern depression, other comorbid clinically significant seasonal pattern depression psychiratric conditions, pregnancy

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Annotations

A. Diagnosis of Major Depression, first episode

OBJECTIVE

To define depression
To present factors which may precipitate or aggravate major depression
To present risk factors for major depression

ANNOTATION

1. Depression is a mood disorder that is primarily characterized by persistent sad or irritable mood and decreased interest or pleasure in a person's usual activities. The principle symptoms of depression may be characterized by specific standardized criteria listed in the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV). See Table 1 below. The prevailing standard for diagnosis of depression is the documentation by a physician that a patient's symptoms meet the criteria described in the DSM-IV.

   Many screening tools are available to help identify patients that may have depression; however, the diagnosis of major depression is confirmed using the DSM-IV criteria. Screening tools may be clinician administered or patient (self) administered. and can vary in length based on the number questions asked. Several of the tools have been tested in the primary care setting, but the sensitivity, specificity and positive predictive value has been variable. The reader may refer to ***The VA/DoD Clinical Practice Guideline for Major Depressive Disorder*** which reviews some of the more commonly used screens such as Primary Care Evaluations of Mental Disorders (PRIME-MD), Center for Epidemiological Studies-Depression scale (CES-D), and Zung Depression Rating Scale.

Table 1. Diagnostic Criteria for Major Depression[a]

A patient must exhibit at least five of the following symptoms during the same 2 week period, and this must represent a change from previous functioning. Symptoms must include either criteria #1 or #2. *Note: A diagnosis of major depressive disorder is made only when the symptoms are not attributable to drugs, a general medical condition, or recent bereavement.*
1. Depressed and/or irritable mood 2. Diminished interest or pleasure in all or almost all of usual activities 3. Significant weight loss or weight gain, or decrease or increase in appetite 4. Insomnia or hypersomnia 5. Psychomotor agitation or retardation as observed by others 6. Fatigue or loss of energy 7. Feelings of worthlessness, or excessive inappropriate guilt 8. Diminished ability to think or to concentrate, indecisiveness 9. Recurrent thoughts of death, suicidal ideation, suicide attempt or a specific plan for suicide

[a] Adapted from DSM-IV

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Depression is a frequently occurring and costly mental health problem present in a significant number of patients seen by primary care physicians. Major depression has a substantial impact on the quality of life and productivity of the patient. Depressed persons frequently present with a variety of physical symptoms; up to three times the number of somatic symptoms of non-depressed patients. The suicide rate in depressed persons is at least 8 times higher than that of the general population. Early detection and intervention of major depression is important in decreasing the severity and duration of depressive episodes.

2. When making a differential diagnosis, there are several factors which may precipitate or aggravate major depressive disorder and should be considered:
   - **life events**: distinguish between minor emotional distress and those which affect interpersonal relationships, impair school or job performance, or trigger suicidal thoughts
   - **medical disorders**: determine whether the mood disorder is due to physiologic consequence of a medical problem (e.g. hypothyroidism, dementia, etc.)
   - **medications**: many drugs may produce depression and/or depressive symptoms and therefore an inquiry about medication use and/or substance abuse is warranted (Refer to Appendix 1)
   - **psychiatric disorders**: disorders such as Dysthymic Disorder, Schizoaffective Disorder, Bipolar Disorder, Posttraumatic Stress Disorder (PTSD), Obsessive Compulsive Disorder (OCD), Dissociative Disorders and Schizophrenia may share some similar qualities as major depressive disorder and should be ruled out.

     Dysthymic disorder is a depressive disorder frequently confused with major depression. Patients with dysthymic disorder share many symptoms with those having major depression, differing only in duration and severity. The essential feature of dysthymic disorder is a chronic mood disturbance (sadness) present most of the time for at least 2 consecutive years. Although the efficacy of antidepressants in dysthymic disorder has not been adequately studied, many patients with this diagnosis will benefit from pharmacological treatment

3. Knowledge of risk factors and recognition of the signs and symptoms of the disease are paramount to accurate diagnosis and treatment:

IDENTIFIED RISK FACTORS INCLUDE[a]:

- **Prior episodes of depression**
- **Family history of depressive disorder**
- **Prior suicide attempts**
- **Female gender**
- **Age of onset under 40**
- **Advanced age**
- **Post partum period**
- **Medical comorbidity**
- **Lack of social support**
- **Stressful life events**
- **Current alcohol or substance abuse**

[a] Adapted from DSM-IV

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4. Address and document DSM-IV criteria for depression (Refer to Table 1).

   Address and document added historical features: duration of symptoms, recent life experiences, alcohol and substance abuse, family history of substance abuse, suicide, depression, previous psychiatric diagnoses/treatment, manic symptoms, suicidal/homicidal ideation or attempts, and review of systemic disease.

   A thorough physical examination is required to sufficiently exclude medical causes of depression, including an examination of skin for evidence of past or present self-inflicted injury and/or substance disorder.

   General appearance, sensorium (orientation, level of consciousness), affect and mood, cognitive function (memory, attention span), speech, thought content and process, perceptual disturbances, judgment, insight, risk of harm to others, or suicidal ideation or intent, should be evaluated to assess mental status.

A thyroid stimulating hormone (TSH) test to rule out thyroid disease is recommended, especially in elderly patients. If diagnosis is uncertain, organic disease is suspected, or patient is elderly also test for the following: erythrocyte sedimentation rate (ESR), complete blood count, electrolytes, serum creatinine, blood urea nitrogen, calcium, phosphate, magnesium, and liver function tests (LFTs).

References:

[1]Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Washington, DE: American Psychiatric Association; 1994

[2]American Psychiatric Association. Practice Guideline for Major Depressive Disorder in Adults. Am J Psychiatry 1993; 150(suppl 4): 1-26

[3]Depression Guideline Panel. Depression in Primary Care. Volume 1. Detection and Diagnosis. Clinical Practice Guideline, No 5. Rockville, MD. U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR Publication No. 93-0550. April 1993

B. Suicide risk/psychosis present?

OBJECTIVE

To identify which patients require referral to a mental health specialist

ANNOTATION

A psychiatric referral should be considered if any of the following is present:

- psychotic features, assaultive behavior, and/or homicidal/suicidal thoughts
- worsening of symptoms despite treatment
- treatment failure after 2 trials of medications in different drug classes
- failure to respond to monotherapy or when higher than recommended doses are needed
- behavioral toxicity (e.g. psychosis, manic episode, memory impairment) which is induced by antidepressant medication
- clinically significant seasonal pattern depression which may require light treatment
- other comorbid psychiatric conditions (e.g. substance abuse, alcoholism, panic disorder)
- pregnancy

References:

[1]Schulberg HC, Katon WJ, Simon GE, Rush AJ. Best Clinical Practice: Guidelines for Managing Major Depression in Primary Care. J Clin Psychiatry 1999;60 (suppl 7):19-26.

[2]Simon GE. Can depression be managed appropriately in primary care? J Clin Psychiatry 1998;59 (suppl 2):3-8.

[3]Depression Guideline Panel. Depression in Primary Care. Volume 2. Detection and Diagnosis. Clinical Practice Guideline, No 5. Rockville, MD. U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR Publication No. 93-0551. April 1993

C. Select and initiate treatment

OBJECTIVE

To assist the practioner in selecting an agent for treatment

ANNOTATION

For the primary care provider, the decision to treat patients with major depression without psychiatric consultation should be based on severity of the depression, associated psychiatric symptoms, and response to initial management. Patients with severe depression, with other psychiatric co-morbid conditions (e.g. alcoholism, bipolar disease) or who have a prior history of psychosis or suicidal ideation or attempts, or who have recurrent depression should be evaluated by a psychiatrist. In general, primary care providers should focus on treating uncomplicated patients with mild to moderate depressive symptoms.

A variety of psychotherapy techniques and electroconvulsive therapy (ECT) are available for the management of depression. Seasonal depression may require light treatment. Psychotherapy by therapists trained in a particular technique (eg. cognitive behavioral therapy), has been shown to be similar to pharmacotherapy for selected patients especially those with mild depression. If the primary clinician is uncertain whether these treatments may be indicated for particular patients, they should obtain a psychiatric consultation.

Many effective agents are available for major depression. Although no one antidepressant medication is clearly more effective than another or results in remission for all patients, there are patient factors and drug side effect profiles that would favor one class of antidepressants over another. The choice of medication is based on side effect profiles (Refer to Appendices 2, 4-8), history of prior response, family history of response, type of depression, concurrent medical illnesses, concurrently prescribed medications, and cost of medication.

Rates of response to antidepressants are reported as high as 60 - 70%. However the rate of complete remission may be substantially lower.[1-3]

The efficacy of selective serotonin reuptake inhibitors (SSRIs) is similar to that of tricyclic antidepressants (TCAs), but the SSRIs have a more favorable adverse effect profile. Due to the low toxicity and ease of administration, SSRIs should be considered first line antidepressants in the primary care setting.[4,5] Although differences in drug characteristics may influence the selection of a specific SSRI for a given patient, there is insufficient evidence to prefer any one SSRI for all patients on the basis of efficacy or side effect profile.[6,7]

Patient and family education about the course and nature of depressive illness, treatment and potential side effects, time course to of symptomatic improvement, and importance of treatment compliance helps to improve treatment adherence and the likelihood of success.

References:

[1]Ferrier IN. Treatment of major depression: is improvement enough? J Clin Psychiatry 1999;60 (suppl 6):10-14.

[2]Nierenberg AA, Keefe BR, Leslie VC, et al. Residual symptoms in depressed patients who respond acutely to fluoxetine. J Clin Psychiatry 1999; 60:221-5.

[3]Fawcett J, Barkin RL. Efficacy issues with antidepressants. J Clin Psychiatry 1997;58 (suppl 6):32-39.

[4]Martin RM, Hilton SR, Kerry SM, et al. General practioners' perceptions of the tolerability of antidepressant drugs: a comparison of selective serotonin reuptake inhibitors and tricyclic antidepressants. BMJ 1997;314:646-51.

[5]Barbey JT, Roose SP. SSRI safety in overdose. J Clin Psychiatry 1998;59 (suppl 15):42-48.

[6]DeJonghe F, Swinkels J. Selective serotonin reuptake inhibitors. Relevance of differences in their pharmacological and clinical profiles. CNS Drugs 1997;7:452-67.

[7]Edwards JG, Anderson I. Systematic review and guide to selection of selective serotonin reuptake inhibitors. Drugs 1999;57:507-33.

D. Monitor and titrate antidepressant therapy

OBJECTIVE
To provide recommendations for patient follow-up once treatment is initiated.

ANNOTATION

It has been shown that up to 50% of patients will stop their antidepressant in the first month, therefore, follow-up is extremely important during the first month of treatment. Reasons for noncompliance include side effects, lack of response, and illness-related parameters such as memory impairment, motivation and apathy, social and cultural influences, and patient perception of the importance and appropriateness of drug treatment.

Ideally, patients should be seen to monitor clinical status and side effects at one week and no later than 2 weeks after antidepressant is started. [QE= III, SR=B][1,2] If the patient cannot be seen during this time frame, contact by telephone may be made. Compliance and patient outcomes are improved if the patient is educated about side effects and the clinician is available to take telephone calls. Thereafter, the patient should ideally be monitored monthly throughout the acute phase of treatment.

Monitor for adverse events and side effects of drugs. Adverse events for individual drugs can be found in appendices 2-8. Gradually increasing the dose may be helpful in minimizing some side effects.

Antidepressants may precipitate manic episodes in bipolar patients, and may activate latent psychosis in other susceptible patients. Close monitoring for any such symptoms may be necessary.

References:
[1]Depression Guideline Panel. Depression in Primary Care. Volume 2. Detection and Diagnosis. Clinical Practice Guideline, No 5. Rockville, MD. U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR Publication No. 93-0551. April 1993

[2]Crismon ML, Rivedi M, Pigott TA, et al. The Texas Medication Algorithm Project: Report of the Texas consensus conference panel on medication treatment of major depressive disorder. J Clin Psychiatry 1999;60:142-56.

E. Assess response in 4-6 weeks

OBJECTIVE
To evaluate patient response during acute phase treatment

ANNOTATION
A response is generally defined as greater than 50% improvement from baseline in depressive symptoms. For some patients, a 50% improvement in symptoms may not be enough, leaving the patient with significant residual symptoms. Therefore, the ultimate goal of therapy is for the patient to be symptom free (remission). The response at 4-6 weeks of treatment is used to assess the efficacy of an antidepressant. [QE= III, SR=B][1,2] Prior to declaring a treatment failure with any antidepressant, it is important to ensure an appropriate target dose range (and plasma level, if established) for the selected medication has been *achieved* (including evaluation of drugs that may increase the metabolism of the antidepressant). The patient should also be evaluated for adherence to therapy and for any side effects to the antidepressant that may influence adherence to therapy.

Some depressive target symptoms (e.g. anxiety, insomnia, decreased appetite, decreased energy, libido) may respond to therapy sooner than the depressed mood resolves. Improvement in psychosocial function may take several months and often lags behind symptomatic improvement.

If the patient has had a full response, the antidepressant is continued for an additional 4-9 months. (see G.)

If a partial response is seen (patient improves significantly but does not fully remit with treatment), continue the same medication for an additional 4 - 6 weeks and then reevaluate. Patients experiencing a partial response after 4 weeks of treatment may go on to have a full response with continued treatment. Ensure that medication is at target dose range to achieve maximum efficacy.

Patients exhibiting no response after 4 weeks of adequate doses of a drug are unlikely to respond to that agent with continued treatment. [QE=II, SR=B] [3-5] Ensure that the diagnosis is current and that medication is at target dose range. The patient's medication regimen should be modified. Options may include, substitution with an alternative agent or combination/augmentation drug therapies. When substituting with an alternative agent, many practioners select an agent from a different class; however, patients may respond to another agent within the same class.[6-10] Consultation with a mental health specialist may be necessary.

References:
[1]Depression Guideline Panel. Depression in Primary Care. Volume 2. Detection and Diagnosis. Clinical Practice Guideline, No 5. Rockville, MD. U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR Publication No. 93-0551. April 1993

[2]American Psychiatric Association Practice Guidelines for Major Depressive Disorder in Adults. Am J Psychiatry 1993;150(suppl 4):1-26.

[3]Quitkin F, McGrath P, Stewart J, et al. Chronological milestones to guide drug change. Arch Gen Psychiatry 1996;53:785-792.

[4]Nirenberg A, McLean N, Alpert J, et al. Early nonresponse to fluoxetine as a predictor of poor 8-week outcome. Am J Psychiatry 1995;152:1500-03.

[5]Boyer WF, Feighner JP. Clinical significance of early non-response in depressed patients. Depression 1994; 2:32-35.

[6]Friedman SJ, Fava M, Kienke AS, et al. Partial response, nonresponse, and relapse with selective serotonin reuptake inhibitors in major depression: a survey of current "next-step" practices. J Clin Psychiatry 2000;61:403-408.

[7]Fava M. Management of nonresponse and intolerance: switching strategies. J Clin Psychiatry 2000;61 (suppl 2):10-12.

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F. Has the patient attained remission

OBJECTIVE
To determine whether a patient enters the continuation phase of therapy or requires modification of therapy

ANNOTATION
Remission can be defined as full resolution of the depressive episode. Patients who have achieved remission are ready to enter the continuation phase of treatment. Patients who have only attained a partial response after 12 weeks of treatment with an antidepressant medication will require a change in therapy. [QE=III, SR=B] [1,2] Treatment options include, substitution with an alternative agent or combination/augmentation drug therapies. Consultation with a mental health specialist is recommended.

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G. Continue medication for an additional 4-9 months

OBJECTIVE
To prevent relapse

ANNOTATION
A relapse is declared if symptoms return within 6 months following acute phase treatment. This phase represents how long a depressive episode would have lasted had there been no treatment. Continuation treatment is aimed at preventing relapse as well as further improving psychosocial functioning. After the acute phase, treatment should be continued with the same drug at the same dose for 4-9 months. [QE=I, SR=A][1-8] If it is determined that drug therapy may be withdrawn after the continuation phase is complete (patient does not require maintenance therapy), it is recommended that the antidepressant be tapered slowly to avoid or minimize symptoms associated with abrupt discontinuation. [QE=III, SR=B][9,10] Agents with long half-lives such as fluoxetine may not require tapering.[11,12] Patients should also be monitored during this time for recurrence of depressive symptoms. **See appendix 9**

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H. Consider maintenance treatment

OBJECTIVE
To prevent recurrence

ANNOTATION

Recurrence is defined as the appearance of a new episode of major depressive disorder, after the patient has fully recovered from a previous episode (more than 6 months after acute treatment). The risk of recurrence increases with each additional episode. A patient whose first episode has been successfully treated has a 50% chance of having a recurrence, a person with 2 episodes has a 70% chance of recurrence, 3 episodes an 80% chance of recurrence, and over 90% after a fourth episode.

Maintenance treatment may be necessary to prevent recurrence. [QE=I, SR= A][1-3] If the patient experiences a recurrence, response to the same medication at the same dosage that was effective previously is likely. Maintenance treatment may be necessary for 1 year or longer. Maintenance treatment studies have not been conducted in the primary care setting therefore; these recommendations are based on data obtained from studies done in the psychiatric patient setting. Studies are not available evaluating maintenance therapy for longer than 5 years.

Recurrence occurs more often in patients with:
• A first degree relative with depression
• The first episode of depression occurring before age 20
• Greater than 2 prior episodes of depression
• A history of recurrence within 1 year after medication was discontinued
• ≥ 2 episodes, and both were severe, sudden, or life-threatening

References:

[1]Keller MB, Kocsis JH, Thase ME, et al. Maintenance phase efficacy of sertraline for chronic depression. JAMA 1998;280:1665-1672.

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Appendix 1. List of medications that may cause depressive symptoms[a]

Corticosteroids	Antilipemic agents
Anabolic steroids	Digoxin
Oral contraceptives	Cycloserine
Interferons	Cimetidine
Angiotensin converting enzyme inhibitors	Metoclopramide
Beta-blockers	Withdrawal from psychostimulants (eg. cocaine, amphetamines)
Methyldopa	
Reserpine	
Clonidine	

[a] List is not all inclusive
[b] Adapted from Patten et al 1997

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Appendix 2. Side Effect Profiles of Antidepressants[a]

0-none +-slight ++-moderate +++-high ++++-very high	Adverse Effects				
	Anticholinergic	**Sedation**	**Orthostatic Hypotension**	**Cardiac Conduction Abnormalities**	**Weight Gai**
TCAs					
Amitriptyline	++++	++++	+++	++++	++++
Desipramine	+	+	+	+++	+
Doxepin	+++	++++	++	++	++++
Imipramine	+++	+++	+++	++++	++++
Nortriptyline	++	++	+	+++	+
Protriptyline	+++	+	++	++++	-
Trimipramine	++++	+++	+++	++++	++++
SSRIs					
Fluoxetine	0/+	0/+	0/+	-	-
Paroxetine	+	0/+	0	-	+
Sertraline	0/+	0/+	0	-	-
Citalopram	0/+	0/+	0/+	-	-
Dual Mechanism					
Bupropion	0/+	0/+	0/+	+	-
Mirtazapine	+	++++	+++	0	++++
Nefazodone	0/+	++	+	+	+
Venlafaxine	0/+	+	0	+	-
MAOIs					
Phenelzine	+	+	++[b]	+	+++
Tranylcypromine	+	+	+[b]	+	++
Other antidepressants					
Amoxapine	+++	++	+	++	++
Maprotiline	++	++	+	++	++
Trazodone	0/+[c]	++++	++	+	++

[a] Adapted from: Hebel SK ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc., 2000

[b] Orthostatic symptoms often appear several days to weeks after treatment is started with MAOIs

[c] Anticholinergic side effects (dry mouth) may be due to a system other than an anticholinergic mechanism

Appendix 3. Relative Inhibition of Newer Antidepressants on CYP450 Isoenzymes[a]

Several of the newer antidepressants interact with the cytochrome P450 isoenzymes. The major ones involved in metabolic reactions such as hydroxylation, demethylation, dealkylation are CYP2D6, CYP3A3/4, CYP1A2, CYP2C9, and CYP2C19. Drugs can act as substrates, inducers or inhibitors of these enzymes. The degree to which a drug can effect an enzyme depends on drug characteristics such as the affinity a drug has to the enzyme and the concentration of drug at the enzyme site. Knowledge of the antidepressant inhibitory profile can be helpful in predicting potential drug interactions with other drugs metabolized by these enzymes.

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0 = minimal or zero inhibition + =mild ++ = moderate +++ = strong - = no data	**Cytochrome P450 isoenzymes**				
	1A2	**2C9**	**2C19**	**2D6**	**3A3/4**
Fluoxetine	+	++	+ - ++	+++	+
norfluoxetine	+	++	+ - ++	+++	++
Sertraline	+	+	+ - ++	+	+
desmethylsertraline	+	+	+ - ++	+	+
Paroxetine	+	+	+	+++	+
Citalopram	+	0	0	0	0
desmethylcitalopram	0	0	0	+	0
Nefazodone	0	0	0	0	+++
hydroxynefazodone	0	0	0	0	+++
Venlafaxine	0	0	0	0	0
o-desmethylvenlafaxine	0	0	0	0	0
Mirtazapine	0	-	-	+	0

Adapted from Greenblatt et al 1998

Appendix 4. Selective Serotonin Reuptake Inhibitors (SSRIs)

The mechanism of action of the SSRIs is selective inhibition of 5HT uptake, with limited affinity for receptors associated with other neurotransmitters. The efficacy of SSRIs is similar to that of TCAs, but the SSRIs have a more favorable adverse effect profile. Due to the low toxicity and ease of administration, SSRIs should be considered first line antidepressants in the primary care setting. SSRIs have a wide therapeutic index and are significantly less likely to be lethal than other antidepressants when taken in overdose. They may be preferred in patients at risk for suicide.

There are presently four agents FDA approved for depression: fluoxetine, sertraline, citalopram and paroxetine. Fluvoxamine is approved only for the treatment of obsessive-compulsive disorder (OCD) and will not be discussed in these guidelines. Patients with obsessive compulsive symptoms should be referred to a psychiatrist.

The elimination half-life and incidence of side effects may vary among SSRIs. The most common side effects include: nausea, insomnia, sedation, headache, dizziness, fatigue, sexual dysfunction, anorexia, sweating, dry mouth, constipation (especially with paroxetine), tremor, nervousness, anxiety (especially with fluoxetine), and diarrhea and loose stools (especially with sertraline). In many cases the side effects can be managed with lower doses and/or concomitant medication. Also, tolerance can develop to some, but not all side effects.

When treatment is initiated, SSRIs may precipitate or exacerbate anxiety and sleep disturbance in some patients. Introducing the agent at a low dose may minimize anxiety. Insomnia may also be effectively treated by low-dose trazodone, or short-term use (1-2 weeks) of lorazepam or diphenhydramine at bedtime. Because of safety concerns, such as addiction, benzodiazepines are generally not a first-choice agent. There are case reports of the precipitation of serotonin syndrome when trazodone and paroxetine are co-prescribed. It is unknown at this time if this is a class effect.

Abrupt discontinuation of SSRIs may precipitate withdrawal symptoms (i.e., vivid dreams, nightmares, tremors, dizziness, nausea, disorientation). Dose should be gradually tapered, especially SSRIs with shorter elimination half-lives and/or no active metabolite.

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Table A. Dosing for SSRIs[a,b]

AGENT	DOSE [c]	DOSAGE ADJUSTMENT
Fluoxetine	**initial** 20 mg/d **range** 20 - 40 mg/d **max** 80 mg/d	• Dosage adjustment not routinely necessary in the elderly or in renal impairment • Patients with hepatic impairment should receive lower or less frequently administered doses • Due to peak effects, administer doses > 20 mg on a once (am) or twice (am, noon) daily schedule
Paroxetine	**initial** 20 mg/d **range** 20 - 50 mg/d **max** 50 mg/d	• For elderly or debilitated patients, renal or hepatic impairment use initial dose of 10 mg/d. increase if indicated to a maximum of 40 mg/d
Sertraline	**initial** 50 mg/d **range** 50 - 200 mg/d **max** 200 mg/d	• Clearance may be decreased in the elderly. May require lower doses • In hepatic impairment use lower or less frequently administered doses • Pharmacokinetics have not been studied in patients with renal impairment; use with caution
Citalopram	**initial** 20mg/d **range** 20-40 mg/d **max** 60mg/d	• No dosage adjustment needed for mild–moderate renal impairment: use with caution in severe renal impairment • 20mg/d is the recommended dose for most patients with hepatic failure or in the elderly

[a] Adapted from Hebel SK ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc., 2000

[b] Semla TP, Beizer JL, Higbee MD. Geriatric Dosage Handbook. 2nd edition 1995-1996. APhA: Lexi-comp Inc., 1995; 301-302, 535-536, 643-644.

[c] Range refers to usual therapeutic range

Table B. SSRI Drug Interactions [a-d]

SSRI	INTERACTING DRUG	DESCRIPTION
Fluoxetine	Diazepam, triazolam, alprazolam, oral midazolam	Clearance of the benzodiazepine (BZD) is decreased. BZD levels and drug effects may increase
Fluoxetine	Buspirone	Effects of buspirone may be decreased. Paradoxical worsening of OCD has occurred although combination has been used to potentiate the antidepressant action of fluoxetine
Fluoxetine citalopram	Carbamazepine	Serum carbamazepine levels may be increased with fluoxetine, which may result in toxicity. Citalopram clearance may be increased.
Paroxetine citalopram	Cimetidine	Cimetidine increases concentration of paroxetine and citalopram; clinical significance unclear
Fluoxetine sertraline	Clarithromycin, erythromycin	Clarithromycin added to fluoxetine has been reported to result in delirium. 2 cases of serotonin syndrome when combining erythromycin and sertraline. Use caution when using SSRIs with macrolide antibiotics
Fluoxetine	Cyproheptadine	Effect of fluoxetine may be decreased or reversed; combination has been used to treat fluoxetine induced sexual dysfunction
Fluoxetine	Phenytoin	Fluoxetine may increase phenytoin level
Paroxetine	Phenytoin	Paroxetine decreases phenytoin levels

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Paroxetine	Phenytoin	Phenytoin decreases half-life of paroxetine
All SSRIs	Warfarin	A pharmacodynamic interaction (↑ bleeding diathesis but unaltered PT) may occur with paroxetine. Concurrent use of sertraline and warfarin result in a relatively small ↑ in PT and delayed normalization of PT. Fluoxetine alone may increase bleeding time
All SSRIs	Lithium	Although a case report suggests that lithium levels may be increased by fluoxetine, neurotoxicity is probably caused by a pharmacodynamic interaction. Lithium is often used to potentiate antidepressant response to SSRIs, but drug combination may warrant a psychiatry consult
All SSRIs	Monoamine oxidase inhibitors (MAOIs)	Refer to **Appendix 7** for drug interaction and washout period
All SSRIs	Tricyclic antidepressants (TCAs)	All the SSRIs have been shown to ↑ desipramine plasma levels and may result in toxicity. Fluoxetine and sertraline may ↑ plasma levels of nortriptyline and imipramine. Combining SSRIs and TCAs may potentiate antidepressant response for SSRIs due to a pharmacodynamic interaction: drug combination may warrant a psychiatry consult
All SSRIs	Sibutramine, selegiline fenfluramine, dexfenfluramine, tramadol, sumatriptan, rizatriptan, naratriptan, zolmitriptan, dihydroergotamine, L-tryptophan, TCAs , MAOIs, venlafaxine, trazodone nefazodone, St. John's wort, mirtazapine, dextromethorphan, meperidine	Symptoms of serotonin syndrome may be precipitated when combining SSRIs with other serotonergic agents
Fluoxetine, paroxetine, sertraline	Clozapine	May ↑ plasma concentration of clozapine. Use combination with caution
Fluoxetine	Digoxin	Case report of increased digoxin concentration
Fluoxetine Paroxetine	Metoprolol, propranolol, carvedilol	Case reports of hypotension, bradycardia, and heart block

[a] Drug Facts and Comparisons. 2000 by Facts and Comparisons, St. Louis, Missouri

[b] Drug Interactions Analysis and Management. Hansten PD, Horn JR eds.; 1999 by Facts and Comparisons, St. Louis, Missouri

[c] Table does not include drug interactions seen with Fluvoxamine

[d] List is not all inclusive

Appendix 5. Tricyclic antidepressants (TCAs)

TCAs are predominately adrenergic reuptake inhibitors. The TCAs are equally efficacious, but do have major differences as reflected in their toxicity profile. (Refer to Appendix 2)

Contraindications to TCAs include:

- Hypersensitivity (cross-reactivity occurs within a chemically related group such as TCAs)
- Acute recovery phase following myocardial infarction (MI)

In general TCAs should be avoided in patients with the following clinical conditions unless consultation from an appropriate specialists guides therapy:

- Angle-closure glaucoma or increased intraocular pressure
- History of urinary retention or uretheral spasm

- Cardiovascular disease (CVD) including coronary heart disease (CHD) with ECG abnormalities, conduction abnormalities including bundle branch block, paroxysmal tachycardia and/or orthostatic hypotension
- Patients at risk for suicide
- Patients with cognitive impairment

The most common side effects include: anticholinergic (dry mouth, blurred vision, increased intraocular pressure, constipation, urinary retention), cardiovascular (orthostatic hypotension, syncope, tachycardia, arrhythmias), CNS (sedation, confusion), weight gain (especially with amitriptyline and doxepin) and sexual dysfunction. TCAs can also decrease seizure threshold.

Despite the possibility of increased toxicity, TCAs may be considered first line agents for certain patients. In general, the secondary amine TCAs (e.g. nortriptyline, desipramine) have equal efficacy and fewer side effects than the parent tertiary amines (e.g. amitriptyline, imipramine).

Use TCAs cautiously in the elderly. If their use is necessary in an elderly patient, nortriptyline and desipramine should be considered first. Due to increased side effects (e.g. CNS, anticholinergic, cardiovascular) associated with amitriptyline, imipramine and doxepin, their use by the primary care physician should be avoided for the treatment of depressed patients > 65 years old.

The clinical value of tricyclic plasma concentrations remains controversial. Plasma levels for desipramine, imipramine, and nortriptyline are best established. Although amitriptyline has been extensively studied, no clear relationship between response and plasma level has emerged. The use of therapeutic blood levels can be of value in particular clinical instances such as in patients who do not respond to or comply with therapy, those on combination therapy, in elderly patients or in patients with suspected drug toxicity.

Therapeutic response and dosing with a TCA may vary among patients due to both pharmacokinetic (e.g. enzyme induction by smoking), and pharmacodynamic (e.g. increased sensitivity in the elderly) differences.

Table A. Dosing for TCAs[a,b]

AGENT	DOSE[c]	DOSAGE ADJUSTMENT
Amitriptyline	**initial** 50-100 mg hs **range** 50-150 mg/day **max** 300 mg/day (reserved for severely ill patients)	Not recommended for use in the elderly
Desipramine	**range** 75-200 mg/day titrate as tolerated (or per levels) **max** 300mg/day (reserved for severely ill patients)	For elderly patients, begin at lower end of range. Range is 25-100 mg/day with maximum at 150mg/day. Serum levels are associated with efficacy Therapeutic level 125 - 300 ng/mL
Doxepin	**initial** 75 mg/day **range** 75-150 mg/day **max** 300 mg/day (reserved for severely ill patients)	Not recommended for use in the elderly

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Imipramine	**initial** 75mg/day **range** 75-150 mg/day titrate as tolerated (or per levels) **max** 250-350mg/d (reserved for severely ill patients)	Not recommended for use in the elderly Serum levels are associated with efficacy Therapeutic level 200-350 ng/mL parent and metabolite (desipramine)
Nortriptyline	**initial** 25 mg tid or 75mg hs **range** 75-150 mg/day titrate as tolerated (or per levels)	For elderly patients, begin at lower doses. Range is usually 30-50 mg/day in divided doses or once daily Serum levels are associated with efficacy Therapeutic level 50 - 150 ng/mL
Protriptyline	**initial** 15-40 mg/day in 3-4 divided doses **range** titrate as tolerated **max** 60 mg/day	For elderly patients, begin initial dose at 5 mg tid. ↑ gradually as tolerated. Monitor cardiovascular system closely at 20 mg/d.
Trimipramine	**initial** 75 mg/day in divided doses **range** 50-150 mg/day (administer at bedtime) **max** 200 mg/day	For elderly patients, begin initial dose at 50 mg/day. ↑ gradually as tolerated. Maximum dose is 100 mg/day.

[a] Adapted from: Hebel SK ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc., 2000

[b] Semla TP, Beizer JL, Higbee MD. Geriatric Dosage Handbook. 2nd edition 1995-1996. APhA: Lexi-comp Inc., 1995.

[c] Range refers to usual therapeutic range

Table B. Therapeutic Drug Monitoring of TCAs [a-c]

- Therapeutic plasma levels for desipramine, imipramine and nortriptyline can be used to guide treatment for patients that do not respond to or comply with therapy, for individuals on combination therapy, in elderly patients, or when ruling out toxicity
- Therapeutic plasma levels should be drawn after 1 week of therapy, when the majority of patients will be in steady state
- Draw blood sample 10-12 hours after the last dose to ensure that absorption and distribution of the drug are complete
- Nortriptyline plasma levels demonstrate a curvilinear concentration-response relationship and therefore the dose should be adjusted to obtain levels within a therapeutic range window (50-150 ng/mL); levels above the upper limit are associated with a declining (but not necessarily toxic) response
- Imipramine (plus metabolite desipramine) plasma levels demonstrate a linear concentration-response relationship and therefore the upper limit is a function of toxicity rather than reduced efficacy (200-350 ng/mL); raising serum levels above threshold may convert nonresponders into responders; monitor for signs and symptoms of toxicity
- The relationship between response and plasma desipramine levels is less clear; in general a minimum levels of 125 ng/ mL should be obtained if tolerated; levels over 300 ng/mL may increase the risk of toxicity

[a] DeVane LC, Jarecke RC. Chapter 33: Cyclic Antidepressants. pharmacokinetics, Principles of therapeutic drug monitoring, 3rd ed., Evans WE, Schentag JJ, Jusko WJ eds.Vancouver, WA: Applied Therapeutics, Inc. 1992:1-47.

[b] Preskorn SH, Burke MJ, Fast GA. Therapeutic Drug Monitoring: Principals and Practice. Psychiatric Clinics of North America. 1993;16(3):611-645.

[c] Charney D, Miller H, Licinio J, Salomon R. Chapter 28: Treatment of depression. From: Schatzberg A, Nemeroff C, ed. Textbook of psychopharmacology. American psychiatric press;1995;575-601.

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Table C. TCA Drug Interactions[a-c]

TCA	INTERACTING DRUG	DESCRIPTION
TCAs	Anticholinergics	Combined use may result in excessive anticholinergic effect
TCAs	Barbiturates	May ↓ TCA serum levels; may have additive central and respiratory effects
TCAs	Carbamazepine	May require larger TCA doses (especially imipramine). Monitor for altered TCA response if carbamazepine therapy is started or discontinued. TCAs may increase carbamazepine serum concentration. Monitor for↑ pharmacologic effects or toxicity
TCAs	Cimetidine	May ↑ TCA serum levels, with ↑ anticholinergic symptoms. May require lower TCA doses. Other H2-antagonists may be better alternatives to cimetidine.
TCAs	Clonidine	Adding a TCA to clonidine may antagonize the hypotensive effect of clonidine. Dangerous elevations in blood pressure and hypertensive crisis have occurred in patients receiving concurrent TCAs. Use caution or avoid co administration
TCAs	Ethanol	Combined use may ↑ impairment in psychomotor skills, especially during the 1st week of treatment.
TCAs	MAOIs	Refer to **Appendix 7** for drug interaction and washout period
TCAs	Phenothiazines	TCAs may ↓ the metabolism of phenothiazines as well as phenothiazines may ↓ the metabolism of TCAs. In combination, monitor ↑ toxicity and altered therapeutic response
TCAs	ALL SSRIs	May ↑ TCA serum level, resulting in toxicity. Use combination cautiously. Start with lower TCAs doses; fluoxetine toxic effects may persist for several weeks after the discontinuation of fluoxetine

[a] Drug Facts and Comparisons. 2000 by Facts and Comparisons, St. Louis, Missouri

[b] Hansten and Horns Drug Interactions Analysis and Management. Hansten PD, Horn JR eds.; 1999 by Facts and Comparisons, St. Louis, Missouri

[c] List is not all inclusive

Appendix 6. Dual mechanism antidepressants

Bupropion

Bupropion is a weak reuptake blocker of 5HT and norepinephrine compared with TCAs, and has some effect of dopamine reuptake. Like most antidepressants, the neurochemical basis of its antidepressant mechanism is not known. Unlike the TCAs, the side effects of bupropion do not include anticholinergic effects. In addition it has little cardiovascular effects, sedation, and sexual dysfunction potential. Bupropion is contraindicated in patients with seizure disorders or diagnosis of bulimia or anorexia nervosa due to increase risk of seizures, although the reported incidence of seizures is less with the new sustained release preparation. Due to a low toxicity profile, it may be considered a good alternative for the elderly.

The daily dose of bupropion should not exceed 450 mg/day for immediate release and 400 mg/day for sustained release. A single daily dose should also not exceed 150 mg for immediate release or 200 mg sustained release as a single dose due to potential for dose-related seizures.

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Nefazodone

Nefazodone is structurally related to trazodone. It works by blocking $5HT_2$ receptors postsynaptically and inhibits 5HT reuptake presynaptically. It also blocks norepinephrine reuptake presynaptically and demonstrates antagonism of α_1-adrenergic receptors. Side effects are dose related. The most common side effects associated with this agent include: somnolence, dizziness, dry mouth, nausea, headache, impaired vision, and constipation.

Nefazodone is an inhibitor of the cytochrome P450 3A4 isoenzyme. Caution should be used when prescribing with drugs that inhibit and/or are metabolized by cytochrome P450 isoenzymes due to potential interactions.

Prior to initiating nefazodone, the washout period after discontinuing an SSRI should generally be 4-5 days for paroxetine, citalopram and sertraline, and several weeks for fluoxetine. If the clinical situation dictates, a shorter washout period may be used. In these cases, the starting dose of nefazodone should be modified, (i.e. 50 mg qd) and then titrated to response as tolerated.

Nefazodone should be considered a second line agent that may be useful in substance abuse patients with anxiety and sleep disorders.

Venlafaxine

Venlafaxine is similar to the TCAs in that it inhibits both NE and 5HT uptake; it has little effect on adrenergic, cholinergic or histaminergic receptors. The most common side effects associated with this agent include: nausea, somnolence, insomnia, dizziness, abnormal ejaculation, headache, nervousness, dry mouth, anxiety, asthenia, and sweating. Venlafaxine treatment has been associated with sustained hypertension. The incidence of increased blood pressure was highest (13%) with doses > 300 mg/day.

Patients on venlafaxine for > 1 week should have their dose tapered prior to discontinuation to avoid withdrawal symptoms. If a patient has been on this agent ≥ 6 weeks, slowly discontinue venlafaxine over 2 weeks.

Venlafaxine is partly metabolized by cytochrome P450 2D6 and therefore the potential exists for enzyme inhibitors to reduce the metabolism of the drug when taken concomitantly.

Venlafaxine should be considered a second line agent.

Mirtazapine

Mirtazapine is a tetracyclic compound unrelated to tricyclic antidepressants. It works by inhibiting presynaptic α_2-adrenoreceptor, which results in an increase in both noradrenergic and serotonergic neurotransmission. It is also a potent antagonist of $5HT_2$ and $5HT_3$ receptors. It may also possess anxiolytic activity.

Adverse effects include: drowsiness, somnolence, fatigue, increased appetite, dry mouth, headache, constipation and weight gain; agranulocytosis has been reported although rare.

Few drug interactions have been reported. Mirtazapine may have additive effects on cognitive and motor performance when given with alcohol and diazepam, and should be used cautiously when combining with other central nervous system depressants.

Mirtazapine should be reserved for patients who are non-responsive to other antidepressants.

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Table A. Dosing for Dual Mechanism Antidepressants[a,b]

AGENT	DOSE[c]	DOSAGE ADJUSTMENT
Bupropion (immediate release/ sustained release)	**initial** 75-100mg bid (immediate release) 150mg qd in am (sustained release) **range** ↑ per response to 300 mg/d in 3 divided doses (immediate release) or 150 mg bid (sustained release) an interval of at least 6 hours should elapse between doses. **max** 450mg/d in 3-4 divided doses (immediate release) or 200mg bid (sustained release)	• Use cautiously in patients with renal or hepatic impairment • For immediate release, an interval of at least 6 hours should elapse between doses. • For sustained release, an interval of at least 8 hours should elapse between doses.
Nefazodone	**initial** 200 mg/d in 2 divided doses **range** 300 - 600 mg/d in 2 divided doses	• In elderly patients initial dose is 100 mg/d in 2 divided doses. May titrate slowly to 300 - 600 mg/d given in 2 divided doses. • No dosage adjustment needed in renal impairment • Area under the curve is ↑ by 25% in patients with cirrhosis. Use with care
Venlafaxine/ Venlafaxine extended release	**initial** 75 mg/d in 2 - 3 divided doses; 75mg once daily (extended release) **range** 150-225 mg/d in 2 - 3 divided doses; 75-225mg once daily (extended release) **max (for moderate depression)** 225 mg/d in 3 divided doses; 225mg once daily (extended release)	• Administer with food • For severely depressed, may ↑ dose to 375 mg/d in 3 divided doses or once daily for extended release • No dose adjustment is necessary for the elderly, but use care individualizing doses • In patients with moderate hepatic impairment: ↓ dose 50%. Patients with cirrhosis may require > 50% ↓ in dose. • In patients with renal impairment (GFR 10 - 70 mL/min): ↓ dose 25%. In patients on dialysis: ↓ dose 50%
Mirtazapine	**initial** 15 mg hs **range** 15-45 mg **max** 45 mg	• Elderly patients and those with moderate-severe renal or hepatic impairment may require lower doses

[a] Adapted from Antidepressants. In: Hebel SK ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc.,2000

[b] Semla TP, Beizer JL, Higbee MD. Geriatric Dosage Handbook. 2nd edition 1995-1996. APhA: Lexi-comp Inc., 1995; 733-734.

[c] Range refers to usual therapeutic range

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Table B. Dual Mechanism Antidepressant Drug Interactions[a-c]

PRECIPITANT DRUG	OBJECT DRUG	DESCRIPTION
Bupropion	Carbamazepine	The plasma concentration of bupropion may decrease. Although this interaction is not well documented, it would be prudent to monitor for altered bupropion response if CBZ is initiated, discontinued, or changed in dosage
Bupropion	Valproic acid	Bupropion may increase serum valproic acid levels
Bupropion	Levodopa	A higher incidence of adverse experiences occurs with concurrent use of these agents. Use small initial doses and small gradual dose increments of bupropion
Nefazodone	Benzodiazepines	Substantial and clinically important increases in plasma concentrations of alprazolam and triazolam have occurred. ↓ initial dose of alprazolam by 50%, ↓ initial dose of triazolam by 75% when coadministered with nefazodone. Lorazepam was not affected
Nefazodone	Haloperidol	Haloperidol clearance was decreased by 35% with no significant increase in peak plasma concentrations or time to peak
Nefazodone	Pimozide	Plasma levels of pimozide may be increased, resulting in QT prolongation or torsades de pointes, sometimes fatal. Do not use concurrently
Bupropion Nefazodone Venlafaxine Mirtazapine	MAOIs	Refer to Appendix 9a for drug interaction and for washout period
Nefazodone	Cisapride[d]	Plasma levels of cisapride, may be increased, resulting in QT prolongation or torsades de pointes, sometimes fatal. Do not use concurrently.
Nefazodone	Digoxin	C_{max}, C_{min} and AUC of digoxin were increased by 29%,27%, and 15% respectively in one study. Monitor digoxin levels
Nefazodone	Simvastatin, lovastatin	Case reports of resultant myositis and rhabdomyolysis when nefazodone added to simvastatin or lovastatin
Nefazodone	propranolol	↓ propranolol concentration. ↑ in m-cpp metabolite of nefazodone. No initial changes in drug dosage necessary; any future changes should be based on clinical response
Nefazodone	Cyclosporine, tacrolimus	May inhibit the metabolism of tacrolimus or cyclosporine

[a] Drug Facts and Comparisons. 2000 by Facts and Comparisons, St. Louis, Missouri

[b] Hansten and Horns Drug Interactions Analysis and Management. Hansten PD, Horn JR eds.; 1999 by Facts and Comparisons, St. Louis, Missouri

[c] List is not be all inclusive

[d] Cisapride was recently withdrawn from the market although it will still be available to select patients through manufacturers patient enrollment program

Appendix 7. Monoamine oxidase inhibitors (MAOIs)

Primary care providers should not prescribe MAOIs (phenelzine, tranylcypromine) or isocarboxazid **unless** they have expertise/experience with these medications.

MAOIs inhibit the enzyme monoamine oxidase, preventing the breakdown of NE, 5HT, and dopamine.

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MAOIs are useful for atypical depression (DSM-IV depression with atypical features). Criteria for atypical depression include reactive mood disturbance, prominent anxiety, histrionic features, phobic features, marked fatigue, reversed neurovegetative features, insomnia combined with hypersomnolence, psychosomatic complaints and/or hypochondriasis.

MAOIs should not be considered first-line for treatment of major depression due to adverse effects and potentially severe drug-drug and drug-food interactions. Fatal hypertensive crisis has occurred with concomitant use of tryptophan or tyramine. These crises usually occur within several hours after ingestion of a contraindicated substance. Serotonin syndrome has also occurred with combination tryptophan or tyramine and MAOI use, and is characterized by mental status changes, myoclonus, hyperreflexia, tachycardia, fever, diaphoresis, shivering, diarrhea, and/or incoordination.

The most common side effects include: orthostatic hypotension, restlessness, insomnia, sexual dysfunction, constipation, nausea, diarrhea, dry mouth, edema, anorexia, dizziness, weight gain (especially with phenelzine), headache, and vertigo.

When changing therapy from a MAOI to another antidepressant or vice versa, a washout period is recommended before starting the new agent. The recommended washout periods are summarized in the table below.

Table A. Recommended Washout Periods with MAOI [a-b]

DRUG	WASHOUT PERIOD WITH AN MAOI
Serious, sometimes fatal, reactions have occurred (i.e., rigidity; hyperthermia; myoclonus; autonomic instability, rapid vital sign fluctuations) as well as mental status changes (i.e., agitation; delirium; coma).	
TCAs	Allow 14 days after stopping an MAOI and before starting medication
SSRIs	Allow 14 days after stopping an MAOI and before starting medication Allow 14 days after stopping sertraline and paroxetine and 5 weeks (due to long half-lives) after stopping fluoxetine before starting an MAOI; in rare cases fluoxetine (plus metabolite) may persist after 5 weeks
Dual Mechanism Bupropion Nefazodone Venlafaxine Mirtazapine	Allow 14 days after stopping MAOI and initiation of treatment with bupropion or mirtazapine Allow 14 days after stopping an MAOI and before starting nefazodone or venlafaxine Allow 7 days after stopping medication and before starting an MAOI
Other Antidepressants Amoxapine Maprotiline Trazodone	Allow 14 days after stopping an MAOI and before starting medication It is not known whether interactions will occur. Although, trazodone has been used safely in combination with MAOIs, caution is still warranted

[a] Adapted from Antidepressants. In: Hebel SK ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc.,2000

[b] Plasma levels may be a useful guide to reduce the possibility of a drug-drug interaction

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Table B. Dosing for MAOIs[a,b]

AGENT	DOSE[c]	COMMENTS
Phenelzine	**initial** 15 mg tid (titrate to at least 60 mg/d) **range** 15-90 mg/d	Use cautiously in the elderly. May need to use lower doses. Maintence doses may be as low as 15mg daily or every other day.
Tranylcypromine	**initial** 10 mg bid **range** 30 mg/d in divided doses **max** 60 mg/d	Use cautiously in the elderly. May need to use lower doses.
Isocarboxazid	**initial** 10mg bid **range** 20-40 mg/d in divided doses **max** 60 mg/d in divided doses	If initial dose tolerated may ↑ dose by 10mg every 2-4 days to achieve dose of 40mg by end of first week of treatment. Use cautiously in the elderly. May need to use lower doses.

[a] Adapted from Hebel SK ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc.,1996: 264s-264x.

[b] Semla TP, Beizer JL, Higbee MD. Geriatric Dosage Handbook. 2nd edition 1995-1996. APhA: Lexi-comp Inc., 1995; 553-54, 707-8.

[c] Range refers to usual therapeutic range

Table C. Foods to avoid while taking MAOIs[a]

Absolutely restricted	Aged cheeses, improperly stored or spoiled meat, fish, or poultry products, aged/cured meats (eg. salami, pastrami, mortadella), marmite, soy sauce, soy bean condiments, broad bean pods (fava beans), tap beer
Moderate use only	No more than 24oz/day of bottle/can beer from major domestic breweries (includes nonalcoholic varieties, red or white wine, soy milk

[a] Adapted from Gardner et al 1996

Table D. MAOI Drug Interactions[a-c]

PRECIPITANT DRUG	OBJECT DRUG	DESCRIPTION
MAOIs	Antidepressants	See first table in Appendix 7 for drug interaction and washout period
MAOIs	Dextromethorphan	Hyperpyrexia, hypotension and death have been associated with this combination
MAOIs	levodopa	Hypertensive reactions occur if levodopa is given to patients receiving MAOIs. Drug interaction is not seen with combination levodopa/carbidopa

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MAOIs	Lithium	Two fatal cases of malignant hyperpyrexia have been reported in patients taking these two agents; causation has not been clearly established. Avoid combination if possible; but if administered, observe closely for malignant hyperthermia.
MAOIs	Meperidine	Co administration may result in agitation, seizures, diaphoresis and fever, progress to coma, apnea, and death. Adverse reactions are possible for weeks after MAOI withdrawal. Avoid this combination; administer other narcotic analgesics with caution
MAOIs	Oral hypoglycemics/ insulin	Excessive hypoglycemia may occur when MAOIs are administered to patients with diabetes. Warn patients on oral hypoglycemics about possible hypoglycemic reactions when MAOI therapy is started. Monitor for deteriorating glycemic control when MAOI is stopped
MAOIs	Sympatho-mimetics	The MAOIs' potentiation of indirect or mixed-acting sympathomimetic substances (including anorexiants), may result in severe headache, HTN, and hyperpyrexia, possibly resulting in hypertensive crisis. Avoid coadministration. Direct-acting agents appear to interact minimally, if at all
MAOIs	L-tryptophan	Coadministration may result in hyperthermia, hyperventilation, increased tone, hyperreflexia, confusion, disorientation, shivering, myoclonic jerks, agitation, amnesia, delirium, hypomanic signs, ataxia, ocular oscillations, Babinski signs, hyperkinesis, and disinhibition. Symptoms appear to resolve upon discontinuation of one or both drugs
MAOIs	Methylphenidate	Co administration may result in hypertensive crisis
MAOIs	Barbiturates	Reduce dose of barbiturate
MAOIs	Beta-blockers	Bradycardia may possibly develop during concomitant use
isocarboxazid	buspirone	Can result in ↑ blood pressure. Allow at least 10 days between discontinuation of isocarboxazid and institution of buspirone
MAOIs	Carbamazepine	Combination may result in hypertensive crisis, severe convulsive seizures, coma, or circulatory collapse
MAOIs	Cyclobenzaprine	Cyclobenzaprine is structurally related to TCAs, therefore use similar caution
MAOIs	Methyldopa	Coadministration may result loss of blood pressure control or signs of CNS stimulation (excitation, hallucination)
MAOIs	Reserpine	Adding reserpine to MAOIs may result in hypertensive reaction
MAOIs	Sulfonamides	Coadministration may result in sulfonamide or MAOI toxicity
MAOIs	Sumatriptan	Combination is contraindicated by manufacturer; can result in ↑ sumatriptan toxicity
MAOIs	Thiazide diuretics	Concurrent use may result in ↑ hypotensive effect
MAOIs	Fenfluramine, dexfenfluramine, sibutramine	May theoretically result in serotonin syndrome
MAOIs	Dextroamphetamine	May result in severe hypertensive reaction
MAOIs	tramadol	Tramadol may ↑ the risk of seizures or serotonin syndrome

[a] Drug Facts and Comparisons. 2000 by Facts and Comparisons, St. Louis, Missouri

[b] Drug Interactions Analysis and Management. Hansten PD, Horn JR eds.; 1999 by Facts and Comparisons, St. Louis, Missouri

[c] List is not all inclusive

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Appendix 8. Other antidepressants

Amoxapine

- Amoxapine is structurally a TCA, but unlike the TCAs, it inhibits the reuptake of norepinephrine, inhibits $5HT_2$ receptors and is an agonist of $5HT_{1A}$ receptors. Amoxapine and/or its metabolites also have postsynaptic dopamine receptor blocking action.
- Amoxapine use should be reserved due to its potential to cause parkinsonian effects, tardive dyskinesia, and rarely neuroleptic malignant syndrome.

Maprotiline

- Maprotiline is a selective inhibitor of NE reuptake.
- Maprotiline is similar to the TCA except that it does not affect reuptake of serotonin.
- Reserve as a second-line agent due to the potential for seizures in both therapeutic doses and overdoses.

Trazodone

- Trazodone weakly blocks 5HT and is a $5HT_2$ partial agonist. Like most antidepressants the neurochemical basis of its antidepressant mechanism is not fully understood.
- Trazodone is not considered a first line agent for major depression, but rather is often used as a hypnotic in patients on SSRIs.
- Unlike the TCAs, it is free from anticholinergic side effects, but still retains the potential to cause orthostasis and a high degree of sedation.
- Although rare, trazodone has been associated with priapism.
- Trazodone may enhance the CNS depressant response to ethanol, barbiturates, and other CNS depressants.
- There have been case reports of serotonin syndrome with co-administration of trazodone and paroxetine. It is unknown at this time if this is a class effect with all SSRIs

St. John's wort

- The use of herbal medications continues to grow in the United States.
- The extract of St. John's wort (Hypericum perforatum L.), an herbaceous plant, has been used to treat mild to moderate depression. It has been compared to placebo, imipramine, amitriptyline, and maprotiline. St. John's wort was found to be better than placebo and as effective as imipramine, amitriptyline, and maprotiline. Some criticisms of these studies are that low doses of tricyclics were used in the comparator trials, the duration of the trials were relatively short (4-8 weeks) and methods of diagnosing depression varied.
- Patients should be asked about herbal medication usage, particularly St. John's wort, in order to avoid inadvertent co-prescribing should use of an antidepressant become necessary.
- Because major depression is a serious condition, patients should be discouraged from self-medicating with St. John's wort.
- Although a promising agent, more information is needed before St John's wort can be recommended as a viable option for the treatment of major depression. Areas requiring further investigation are trials using standard doses of the comparator, use of the newer antidepressants as comparators, long-term trials, and use of standard criteria (DSM-IV) for diagnosing depression.
- St. John's wort may induce the CYP 3A4 isoenzyme and the intestinal P-glycoprotein drug transporter. There have been examples in the literature of reduced plasma concentration of indinavir, cyclosporine, digoxin, and oral contraceptives which may be explained by one or both of the above described mechanisms.
- The usual dose of St. John's wort is 300mg tid (standardized to 0.3% hypericin).

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Dosing Table for Other Antidepressants[a,b]

AGENT	DOSE[c]	
Amoxapine	**initial** 50 mg bid or tid **range** 200-300 mg/day **max** 400-600 mg/day if no history of seizures (reserved for severely ill patients)	In elderly patients begin dosing at 25 mg bid or tid; if tolerated , may ↑ to 50 mg bid or tid in first week. The usual range is 100-150 mg/day. The maintenance dose usually yields adequate control but some may need higher doses For the adult dosage, may ↑ dose to 100 mg bid or tid in first week May give as single dose once effective dosage is established. Do not exceed 300mg as single dose.
Maprotiline	**initial** 75 mg/d as a single or divided doses **range** 150 mg/d **max** 225 mg/d	In elderly patients begin dosing at 25 mg/day in single or divided dose. The usual range is 50-75 mg/day
Trazodone	**Initial** 150 mg/day in divided doses **range** 150-400mg/day in divided doses **max** 600 mg/d in divided doses (reserved for severely ill patients)	In elderly patients begin dosing at 25 - 50 mg at bedtime. The usual range is 75 - 150 mg/day.

[a] Adapted from Antidepressants. In: Hebel SK ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc.,1996

[b] Semla TP, Beizer JL, Higbee MD. Geriatric Dosage Handbook. 2nd edition 1995-1996. APhA: Lexi-comp Inc., 1995; 46-47, 98-99, 432-433, 709.

[c] Range refers to usual therapeutic range

Appendix 9. Antidepressant taper

- Discontinuation syndrome has been reported with TCAs, SSRIs, MAOIs, venlafaxine, and nefazodone when therapy is abruptly stopped or less commonly when dosage is reduced. Agents with a long half-life such as fluoxetine, may not require dosage tapering.
- Generally, a 4-6 week taper is adequate; however, the rate should be individualized with consideration given to drug, dose, and duration of therapy.
- Symptoms of the discontinuation syndrome include: anxiety, irritability, flu-like symptoms, dizziness/disequilibrium, paresthesias, lethargy, insomnia, vivid dreams and nightmares.
- Generally, symptoms begin 24-72 hours after the last dose and may last for 1-2 weeks.
- The majority of cases are mild and self-limited in nature requiring only patient reassurance. Severe cases require reinstitution of dosage and a yet slower taper with symptoms usually resolving within 24 hours.

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