

## CLINICAL GUIDELINE, PART 1

## Pharmacologic Treatment of Acute Major Depression and Dysthymia

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*The numbers in square brackets are cross-references to the numbered sections in the accompanying background paper, "A Systematic Review of Newer Pharmacotherapies for Depression in Adults: Evidence Report Summary," which is part 2 of this guideline (see pages 743-756).*

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For current author addresses, see end of text.

For definitions of terms, see Glossary at end of text.

**M**ajor depression and dysthymia are two of the most common and debilitating illnesses. The World Health Organization estimates that worldwide, major depression is the fourth leading cause of loss of disability-adjusted life-years. Major depression is a clinical syndrome lasting at least 2 weeks, during which the patient experiences either depressed mood or anhedonia plus at least five of the following symptoms: depressed mood most of the day, nearly every day; markedly diminished interest or pleasure in most activities most of the day; significant weight loss or gain or appetite disturbance; insomnia or hypersomnia; psychomotor agitation or retardation; inappropriate guilt; diminished ability to think or concentrate, or indecisiveness; or recurring thoughts of death, including suicidal ideation. Dysthymia, by contrast, is a chronic but mild depressive disorder found in approximately 3% of community populations. It also causes significant impairment and is characterized by depressed mood, less severe than that in major depression, that is present on more days than not for 2 years. During this period, two of the following symptoms must also be present: appetite disturbance, insomnia or hypersomnia, decreased energy or fatigue, low self-

esteem, decreased concentration or difficulty making decisions, or feelings of hopelessness.

This guideline is based on an evidence report on pharmacotherapies for depression from the San Antonio Evidence-based Practice Center that was commissioned by the Agency for Healthcare Research and Quality (1). It answers the following questions: What is the evidence supporting the benefits of pharmacologic treatment? What are the data on the efficacy and side effect profiles of "newer" compared with "older" pharmacotherapies? How can the evidence assist physicians and patients in making informed decisions about treatment options?

The lifetime risk for major depressive disorder ranges from 10% to 25% for women and 5% to 12% for men, with a point prevalence rate of 5% to 9% for women and 2% to 3% for men. Persons of all ages, ethnicities, and socioeconomic status experience the burden of depression. The prevalence of depressive disorders varies; it is lowest in community samples, intermediate in outpatient populations, and highest in inpatient settings. Because of the increasing prevalence of depression worldwide, especially in elderly persons, primary care physicians can expect to encounter and screen more patients with this condition (2) [2.2].

Three types of therapies have proven efficacy for depressive disorders: pharmacotherapy, psychotherapy, and electroconvulsive therapy. Because pharmacotherapy is the main tool of the primary care physician, it forms the focus of this guideline.

Clinicians are faced with a multitude of antidepressants to choose from. These include "older" agents, such as the first- and second-generation tricyclic antidepressants, heterocyclics, and monoamine oxidase inhibitors. During the past decade, several "newer" classes of antidepressants have become available. The most notable of these is selective serotonin reuptake inhibitors (SSRIs). Lesser-known new agents include serotonin and noradrenaline reuptake inhibitors; selective norepinephrine reuptake inhibitors; reversible inhibitors of monoamine oxidase; 5-hydroxy-tryptophan<sub>2</sub> (5-HT<sub>2</sub>) receptor antag-

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onists; 5-HT<sub>1a</sub> receptor agonists;  $\gamma$ -aminobutyric acid mimetic agents; dopamine reuptake inhibitors; dopamine antagonists; and herbal remedies, such as hypericum (St. John's wort). In general, clinicians believe that the newer antidepressants, particularly SSRIs, are more efficacious, have a more benign side effect profile, and are better tolerated by patients.

The San Antonio Evidence-based Practice Center found a sufficient number of randomized, controlled clinical trials and meta-analyses to evaluate the efficacy of treatment of acute major depression and dysthymia. The researchers systematically reviewed the literature and gathered evidence from 315 trials selected from 1277 relevant citations. The evidence was sufficient to evaluate treatment in adult primary care settings and in elderly patients with no comorbid conditions, but it was insufficient to evaluate treatments of other depressive disorders, such as subsyndromal depression and refractory depression. Similarly, evidence was insufficient to evaluate the treatment of depression in adolescents or patients with comorbid psychiatric conditions [1].

The primary outcome measures used in the clinical trials to assess drug efficacy were scores on the Hamilton Rating Scale for Depression, the Montgomery Asberg Depression Rating Scale, or the Clinical Global Impression Scale. These scales provide valid and reliable assessment of severity of depression and treatment-associated variations in severity. Most studies did not assess functional status or quality of life. Clinical improvement was defined as a 50% or greater improvement in score on the Hamilton Rating Scale for Depression or Montgomery Asberg Depression Rating Scale or "much to very improved" on the Clinical Global Impression Scale. The Evidence-based Practice Center computed response rates by using a modified intention-to-treat approach, in which the number of patients who continued treatment and got better was divided by the total number of patients who were randomly allocated. This method produces a conservative estimate of treatment effect because some patients who discontinued treatment may have improved.

### Is Pharmacologic Treatment of Depression Beneficial?

Previous systematic reviews of the literature have shown that first- and second-generation tricyclic antidepressants are more efficacious than placebo for treating mood disorders (3). The Evidence-based Practice Center report found evidence that valid conclusions could be drawn about the comparative efficacy of SSRIs, serotonin and noradrenaline reuptake inhibitors, reversible inhibitors of mono-

**Table. The 11 Most Common Adverse Effects of Selective Serotonin Reuptake Inhibitors and Tricyclic Antidepressants**

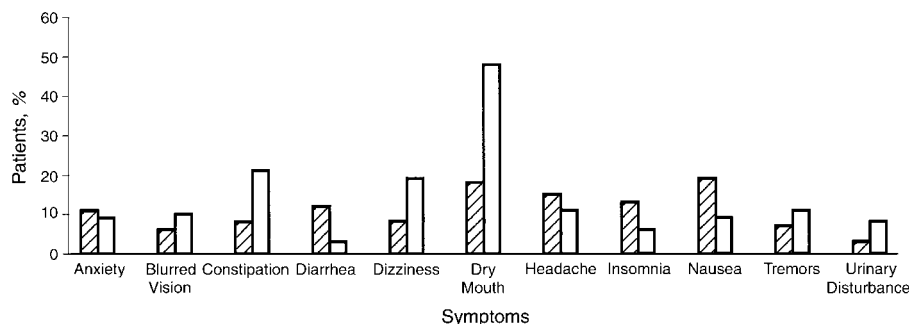
Adverse Effect	Rate with Selective Serotonin Reuptake Inhibitors	Rate with Tricyclic Antidepressants	Difference (95% CI)
	%	%	percentage points
Anxiety	11.00	9.00	2.00 (-2 to 6)
Blurred vision	6.00	10.00	-4.00* (-5 to -1)
Constipation	8.00	21.00	-12.00* (-14 to -7)
Diarrhea	12.00	3.00	10.00* (53 to 13)
Dizziness	8.00	19.00	-11.00* (-13 to -16)
Dry mouth	18.00	48.00	-30.00* (-33 to -23)
Headache	15.00	11.00	3.00* (2 to 4)
Insomnia	13.00	6.00	7.00* (32 to 8)
Nausea	19.00	9.00	10.00* (6 to 11)
Tremors	7.00	11.00	-4.00* (-5 to -1)
Urinary disturbance	3.00	8.00	-5.00 (-8 to -1)

\* Statistically significant.

amine oxidase, 5-HT<sub>2</sub> receptor antagonists, and St. John's wort. Compared with placebo, treatment with these classes of drugs resulted in clinically and statistically significant improvement of acute major depression [2.2.1, 2.5.1]. In primary care settings, the average treatment response difference was 25%, and in elderly persons without comorbid conditions, the difference was 20%. The combined average treatment response difference was approximately 20%. In addition, for treating dysthymia, the effect difference of SSRIs compared with that of placebo (59% and 37%) was clinically and statistically significant [2.4.1].

### Are Newer Drugs or Herbs Better Than Older Drugs in Treating Depression?

In 150 clinical trials involving more than 16 000 participants, 154 comparisons were made between newer and older antidepressants [2.2.2]. Fifty of these studies compared SSRIs with first- and second-generation tricyclic antidepressants [2.2.2], 14 studies compared two SSRIs [2.2.3], and 14 studies involving more than 1400 patients compared St. John's wort with placebo and first-generation tricyclic antidepressants [2.5.1]. No clinically or statistically significant differences in efficacy were found within SSRIs or between SSRIs and tricyclic antidepressants for treatment of major depression. However, for treating dysthymia, sufficient evidence was available for evaluation of only two SSRIs—fluoxetine and sertraline—and for ritanserin, a 5-HT<sub>2</sub> receptor antagonist that is not available in the United States [2.4.1]. St. John's wort has been shown to be more efficacious than placebo; whether it is as efficacious as tricyclic antidepressants given in adequate doses has not been established. Dosages



**Figure.** Adverse effects of selective serotonin reuptake inhibitors (striped bars) and tricyclic antidepressants (white bars).

of tricyclic antidepressants may have been subtherapeutic, and statistical evidence indicated publication bias in the St. John's wort studies.

### Side Effect Profiles and Patient Preference

Selection of antidepressant agents is based in part on such criteria as anticipated tolerance and adverse effects. In the clinical trials, overall dropout rates did not differ significantly between active treatments. The rate of dropout due to adverse effects was slightly higher (and statistically significant) for first-generation tricyclic antidepressants than for SSRIs (16% compared with 11%; difference, 5 percentage points [95% CI, 2 to 6 percentage points]). No differences in adverse effect-related dropout rates were found between second-generation tricyclic antidepressants and SSRIs. Only 1.5% of persons taking St. John's wort discontinued use because of adverse effects, which were not well described. In this review, adverse effects were assessed and reported by using different methods, and few trials differentiated emergent from preexisting symptoms [2.2.4]. The **Table** lists the 11 most common adverse effects found for SSRIs and tricyclic antidepressants.

Rates of blurred vision, constipation, dizziness, dry mouth, and tremors were significantly higher with use of tricyclic antidepressants. Rates of diarrhea, headache, insomnia, and nausea were significantly higher with use of SSRIs (**Figure**). Evidence indicates that some adaptation to nausea and dizziness occurs after 4 to 6 weeks of treatment with SSRIs (4). In clinical practice, patients report that sedation is also a common side effect, but it was not mentioned in the studies [2.2.4].

Other important side effects of both classes of drug include sexual dysfunction and suicide attempts. Fewer than 10% of the trials explicitly reported suicide attempts and suicides. In all, 19 suicide attempts and 15 suicides were described. Because of small numbers, these events were not compared among drug classes. In 11% of the trials, diverse types of sexual dysfunction were reported, including

nonspecific sexual problems, ejaculatory abnormality, decreased libido, male impotence, erectile dysfunction, and anorgasmia. The data were insufficient to estimate incidence rates, thus making quantitative comparisons among antidepressants impossible [2.2.4].

Nine uncommon (<1% occurrence) but serious adverse effects were associated with SSRIs: bradycardia, bleeding, granulocytopenia, seizures, hyponatremia, hepatotoxicity, the serotonin syndrome, extrapyramidal effects, and mania in unipolar depression. Serious adverse effects of tricyclic antidepressants were orthostatic hypotension, the neuroleptic malignant syndrome (similar to the serotonin syndrome), decreased seizure threshold, and cardiac arrhythmias. St. John's wort was not associated with any serious adverse effects [2.5.1]. Unfortunately, clinicians do not report every adverse effect they encounter. Studies have estimated that practitioners report only 1 serious adverse effect for every 100 to 4600 they encounter.

### Recommendations

1. For primary care patients with acute major depression or dysthymia, including elderly persons without significant comorbid conditions, physicians should consider either tricyclic antidepressants or newer antidepressants, such as SSRIs, as equally efficacious treatments. For short-term treatment of mild acute depression, St. John's wort may be considered, but patients should be cautioned that this treatment is not approved by the U.S. Food and Drug Administration and that preparations may vary substantially from those tested in randomized trials.

A key issue in antidepressant therapy is achieving a therapeutic dose for an adequate time period. One primary care-based effectiveness study—that is, of treatment under normal clinical conditions—addressed this issue (5). This study randomly assigned volunteer patients to groups that received tricyclic antidepressants or SSRIs; both groups were treated by their regular physicians. The participants and their physicians decided dosages and drug

changes. No treatment guidelines were used, nor were any data collected on reasons for dosage or drug changes. Slightly more participants changed from tricyclic antidepressants to SSRIs. The study found no difference in overall depression outcomes or health care costs, even though SSRIs were up to 10 times more expensive than tricyclic antidepressants (6). This finding may be attributable to more physician visits being required by patients using tricyclic antidepressants. The literature indicates that the dosage of tricyclic antidepressants must be titrated, whereas the therapeutic dose for SSRIs is usually the initial dosage. Self-titration may reduce or eliminate the difference found in office visits.

2. *Because older and newer antidepressants are equally efficacious, the physician and patient should jointly review the adverse effect profiles of both drug classes so that an agent that fits the clinical needs of the patient can be chosen.*

As with any therapeutic decision in which several options may be equally efficacious, the physician and the patient must discuss other factors influencing drug choice. These factors include possible adaptation to some adverse effects and patient tolerances and preferences for different side effects. The more rare but serious adverse effects, such as orthostatic hypotension and cardiac arrhythmias, are particularly important when choosing an agent for elderly persons and patients with comorbid conditions. Patient education and close follow-up (at least every 2 weeks during initial treatment) should be provided to maximize adherence to therapy and to monitor treatment effects, because patients often discontinue antidepressant therapy prematurely.

3. *Antidepressant medication should be continued at the same dose for at least 4 months beyond initial recovery or improvement to decrease the probability of short-term relapse. If at 6 weeks a patient shows no response or a poor response to an adequate dose of antidepressant medication, treatment should be changed.*

In randomized trials, beneficial treatment effects have been seen by 6 weeks of therapy. Trials of longer duration did not show increased benefit, suggesting that patients who have not responded by 6 weeks are unlikely to benefit from continued medication at the same dose. It is uncertain whether a change of drug classes or within classes is most effective. Approximately 35% of patients who discontinue antidepressant medication will experience relapse within 6 months. The greatest risk seems to be in the first 2 to 4 months after recovery. Maintenance therapy with tricyclic antidepressants decreases the risk for relapse, and of the newer drug classes, only SSRIs (citalopram, fluoxetine, paroxetine, and sertraline) have been shown to decrease the relapse rate for up to 6 months. Most studies reported maintenance-phase doses to be the same

as or higher than the initial dose to which the patient responded [2,3]. Still, few data address the efficacy of longer-term maintenance therapy. A recent randomized, controlled trial of patients older than 59 years of age compared nortriptyline and interpersonal psychotherapy, alone and in combination, as maintenance therapies for recurrent major depression. The study concluded that patients who received both nortriptyline and interpersonal psychotherapy had significantly lower recurrence rates after 3 years than those who received drug therapy or interpersonal therapy alone (7). Physicians should also be aware that when they discontinue therapy with SSRIs, titrating the dosage downward is necessary to avoid withdrawal symptoms, such as delirium, mania, and postural hypotension.

4. *Physicians should ensure that every instance of a serious adverse effect is accurately reported to the U.S. Food and Drug Administration in a timely manner, either through their Web site at [www.fda.gov/medwatch/report](http://www.fda.gov/medwatch/report), by telephone at 800-FDA-1088, or by fax at 800-FDA-0178.*

Because the current rates of reporting adverse events ranges from 1 in 100 to 1 in 4600 incidents, the cumulative effect of nonreporting may lead to misconceptions about the safety of a pharmaceutical agent, possibly resulting in unnecessary suffering and deaths. Adverse events caused by herbal products can also be reported by using the above numbers.

5. *Future studies should include measures of functional status and quality of life. Patients, therapists, and settings should be clearly described. Studies should include information on relapse prevention and long-term maintenance. Studies should be conducted on diverse patient categories, including patients with comorbid medical conditions, refractory depression, and other depressive disorders. Studies of St. John's wort should include more detailed reporting of adverse effects, standardized dosing, effects of long-term therapy, and comparisons with newer agents. More studies are needed on psychotherapy in conjunction with pharmacologic therapy for acute-phase and long-term treatment.*

## Glossary

*Effectiveness:* A measure of the extent to which a specific intervention, when used in the field, does what it is intended to do for a specified population.

*Efficacy:* A measure of the extent to which a specific intervention produces a beneficial effect under ideal conditions. Ideally, the determination of efficacy is based on the results of a randomized, controlled trial.

*Mild depression:* Episodes of a major depressive disorder whose severity is characterized by the presence of 5 to 6 depressive symptoms and either mild disability or the capacity to function normally, but with a substantial and

unusual effort. Also defined as a score of 7 to 17 on the Hamilton Depression Rating Scale.

*Moderate depression:* Episodes without psychotic features that occur in a major depressive disorder. Symptoms are midway between mild and severe, or patients have a score of 18 to 24 on the Hamilton Depression Rating Scale. (Scores of more than 17 are often used as the threshold for including patients in trials.)

*Point prevalence:* The number of people with a condition (or attribute) at a specified point in time.

*Severe depression:* Characterized by the presence of most of the symptoms of major depression and a clear-cut, observable disability, such as the inability to work or care for children, or a score of 25 or greater on the Hamilton Depression Rating Scale.

*Addendum:* Since the writing of this guideline, two important studies on St. John's wort appeared in the literature. These studies found that St. John's wort significantly decreases serum levels of indinavir and cyclosporine. The mechanism for this decrease is induction of the cytochrome P450 system. Thus, it is logical to presume that St. John's wort affects plasma concentrations of all drugs that are metabolized by the cytochrome P450 system. Although this guideline excludes patients with comorbid conditions, physicians and patients must take this new knowledge into account.

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