Achieving the best outcome in treatment of depression

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Practice recommendations

- Combined treatment with psychotherapy or psychiatric consult and drug therapy has shown better response in several studies than either therapy alone (A).
- Although not proven by clinical trials, selecting a medication by matching its side-effect profile to patient characteristics is supported by case reports and likely enhances compliance.
- Patients who do not improve with initial therapy often benefit from being switched to another class of antidepressants (A), or having a drug from another class added to their therapy (B).

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You are more likely to see depression in your practice than any other disorder except hypertension.[1] Given the prevalence of depression* and the variability of its clinical symptoms and comorbidities, how do you determine the optimal therapy for a given patient?

A sobering thought: nearly half of all patients stop taking their antidepressant prescription medication within the first month of treatment.[1] We discuss the critical factors you can address to help patients stick with treatment and achieve the best outcome.

THERAPEUTIC OPTIONS

Pharmacotherapy

Antidepressants are thought to exert their therapeutic and adverse effects through 3 chemical monamine neurotransmission systems; by increasing levels of norepinephrine, serotonin, or dopamine in the synapse; and by resultant secondary changes in presynaptic and postsynaptic receptor physiology.[3,8,9] Newer medications—such as selective serotonin reuptake inhibitors (SSRIs)—have simpler dose schedules, different

** For a review of screening for depression, see Nease DE, Malouin JM. Depression screening: A practical strategy. J Fam Pract 2003; 52(2):118–126.*

The burden of depression

At any one time, at least 3% of the US population suffers from chronic depression.[2] More than 17% of the population have had a major depressive episode in their lifetime, and more than 10% have experienced an episode within the past 12 months.[3] The incidence and prevalence of depression in women are approximately twice that seen in men.[4]

Major depression is the fourth leading cause of worldwide disease burden.[5]

Natural history and prognosis

An untreated episode of depression usually lasts 6 months or longer. About half of persons experiencing major depression will have a second episode; a second episode increases the risk for a third episode to 80%.[1,3] Patients diagnosed with depression average 5 depressive episodes in their life and may have recurrences every 4 to 6 years. Episodes usually become longer and more frequent with advancing age. In about 20% to 35% of cases, only partial remission occurs and functioning remains impaired.[1]

Fifteen percent of severely depressed patients commit suicide. The 2 most powerful predictors of suicide are a history of major depression or schizophrenia and a history of addictive disorders.[6]

Outpatient treatment of depression has increased markedly in the United States, with greater involvement on the part of physicians, greater use of psychotropic medications, expanding availability of third-party payment, and less use of psychotherapy.[7]

(and for some patients more favorable) adverse effect profiles, and less likelihood of causing death from overdose compared with older tricyclic antidepressants (TCAs) and monamine oxidase inhibitors (MAOIs).

Patients are less likely to discontinue treatment with SSRIs than with TCAs (odds ratio=1.21; 95% confidence interval [CI], 1.12–1.30).[10]

However, there are no clinically significant differences in effectiveness between SSRIs and TCAs (strength of recommendation [SOR]: **A**).[11] Importantly, although practice patterns in the use of antidepressants have changed, some reasons for the preference of newer effective agents have not been substantiated. For instance, we do not know whether the patient population taking newer agents has a lower rate of suicide, despite the difference in fatality risk mentioned earlier.

Combined pharmacotherapy and psychiatric consultation

Combining pharmacotherapy and psychotherapy can be more effective than either modality alone. In one study, 73% of patients with chronic depression treated with combination therapy showed a reduction of 50% or more on the Hamilton Rating Scale for Depression (HRSD), compared with just 48% in the nefazodone-only and psychotherapy-only groups (SOR: **A**). Among those who completed the study, the rates of response were 85%, 55%, and 52%, respectively (although the results considered compliant patients only, which biases the results in favor of treatment).[2]

Among elderly depressed patients who received home care, 58% of those who underwent intervention by a psychogeriatric team recovered, compared with just 25% in the control group (SOR: **A**).[12] The intervention group received a multidisciplinary team evaluation and an individualized management plan, which could include any combination of physical, psychological, or social interventions. The control group received usual care from their general practitioner.

Studies of combination therapy have yielded mixed results, but guidelines from the psychiatric literature based on clinical experience advocate

concomitant psychotherapy and medication (SOR: **A**).[13] For patients with persistent symptoms after 6 to 8 weeks of taking antidepressant medication, concomitant psychotherapy improved compliance, satisfaction, and outcomes when compared with usual care.[14]

The concomitant therapy group participated in a multifaceted program including education, psychiatric referral, pharmacy utilization records, and primary physician feedback. The usual care group received standard antidepressants and follow-up visits from their family physician, with optional referral to a mental health provider.

Psychotherapy has also been shown to decrease the risk of relapse once symptoms have remitted.[15] Primary care physicians can also incorporate counseling as adjunctive therapy.

Herbal and nutritional products

St. John's wort. St. John's wort (*Hypericum perforatum* L.) has been used as an herbal medication for more than 2000 years. Its efficacy in the treatment of depression has been studied extensively. Some studies demonstrated that these extracts are more effective than placebo for the short-term treatment of mild and moderate depression.[16,17,18] Two randomized controlled trials demonstrated minimal efficacy of St. John's wort in moderately severe major depression.[19,20] The National Institutes of Health is sponsoring a placebo-controlled, double-blinded trial comparing St. John's wort with SSRIs.[21]

Omega-3 fatty acids. Chronic deficiencies of essential fatty acids may adversely affect central nervous system function. In a small, 4-week double-blind study, outpatients receiving antidepressant therapy who were also given eicosapentaenoic acid exhibited improvement in core depressive symptoms (eg, worthlessness, guilt, insomnia) compared with the antidepressant-plus-placebo group. Larger, long-term prospective trials are needed to confirm an antidepressant effect with omega-3 fatty acids.[22]

S-adenosyl-L-methionine. S-adenosyl-L-methionine is possibly effective for short-term treatment of major depression. Data for other herbal or nutritional remedies are negligible.[23]

Although many patients settle for partial improvement, the treatment goal should be complete remission

Exercise

Physical activity may play an important role in relieving depression. One randomized controlled trial showed that an aerobic exercise program, sertraline therapy, or a combination of both were equally effective in the treatment of depression, although there was a more rapid initial response with sertraline.[24]

A systematic review and meta-analysis concluded that exercise may reduce depression symptoms short term, but much of the evidence is of poor quality.[25] Well-controlled studies are needed to clarify the role of exercise in the treatment of depression. However, exercise is promising enough to consider implementation in clinical practice at this time.

TREATMENT STRATEGY

Guidelines for medicating patients and setting expectations

Start antidepressant therapy promptly when depression is diagnosed. Maintain the initial dosage for at least 3 to 4 weeks before increasing it. A trial of 6 to 8 weeks at maximum dosage (or the maximum tolerated dosage) is necessary to confirm treatment success or failure.[26,27,28]

An improvement in symptoms will usually not be noted until after 2 to 6 weeks of therapy. Depending on depression severity, schedule weekly or monthly visits for patients during the initial treatment phase. The response rate to initial treatment is only 50% to 60%, but more than 80% of depressed patients will respond to at least 1 medication.[1]

Response to placebo is highly variable. It is often substantial and has increased in recent years. In an analysis of 75 trials between 1981

and 2001, the mean proportion of patients in the placebo group who responded (≥50% improvement on the HRSD) was 29.7%, compared with 50.1% in the active medication group.[29] The placebo effect may reflect some combination of patient expectations, the natural history of depression with possible spontaneous remission, and limitations of study methods.

Antidepressant therapy is effective compared with placebo for depression secondary to medical illness (number needed to treat [NNT], 4.2; 95% CI, 3.2–6.4), with minimal treatment dropout (number needed to harm, 9.8; 95% CI, 5.4–42.9).[30] Although many patients settle for partial improvement of their symptoms, the treatment goal should be complete remission.

Factors in drug selection

Selecting an antidepressant can be challenging: more than 24 drugs are on the market, each working through 1 or more of 7 pharmacologic mechanisms. Theoretically, choosing a drug is made easier by matching patient symptoms to likely medication side effects or by knowing that the patient or a family member responded favorably to a particular antidepressant in the past.

This intuitive model has not been proven superior to any other model of selecting antidepressants, but it is clinically sound, pharmacodynamically appealing, and supported by case reports. Its strength may lie in enhancing patient adherence during the critical initial phase of treatment.

A recent randomized, prospective comparison of the SSRIs paroxetine, fluoxetine, and sertraline showed similar effectiveness and tolerability (SOR: **A**).[31] This suggests that efforts to individualize therapy based on comorbidities or likely side effects may not be as useful when choosing from among analogous SSRIs.

Nevertheless, choosing a drug that is effective, convenient, and well tolerated will improve the likelihood of achieving and maintaining a full remission. The data on adverse effects of antidepressants are widely available and well understood. Also consider cost (**Table**).

Preferences based on characteristics. For a patient whose depression is not complicated by other clinical conditions, the initial choice of antidepressant would usually be an SSRI. But nefazodone, mirtazapine, bupropion, or low-dose venlafaxine may be equally appropriate.

For a patient whose depression has other specific components, use your knowledge of drugs' common side effects to fit the patient's clinical profile.

- If there is generalized anxiety, agitation, and insomnia, both nefazodone[8] and mirtazapine[32] are excellent choices. Trazodone at low doses is often used as a sedative with nonsedating antidepressants.[8]
- If weight gain is desired, mirtazapine is indicated.[32]
- If tobacco cessation is a secondary goal, bupropion is preferred.[31]
- Those suffering from hypersomnia, retarded depression, cognitive slowing, and pseudodementia would benefit from bupropion or venlafaxine.[9]
- For more severely depressed patients, venlafaxine may be advantageous due to its dual serotonergic and noradrenergic activity at moderate to high doses.[34,35,36] Mirtazapine and TCAs are also useful in severe depression, as well as for coexisting chronic pain syndromes.[8] For refractory or atypical depression in motivated and compliant patients, MAOIs my be useful.[8]

When to avoid specific drugs.

- Patients with hypersomnia and motor retardation should avoid nefazodone and mirtazapine.[8,32]
- With obesity, mirtazapine and TCAs are least preferred.[8,32]
- If sexual dysfunction preceded depression, avoid giving SSRIs and venlafaxine.[3]
- Those experiencing agitation and insomnia should avoid bupropion and venlafaxine.[3]
- Seizure disorder is a contraindication to bupropion.[3]
- Hypertension is a relative contraindication to venlafaxine.[3]
- Liver disease is a contraindication to nefazodone.[37]

TABLE

Comparative dosages and costs of antidepressant drugs

Agents	Initial target dose	Maximum effective dose	Monthly cost of initial target dose*
Selective serotonin reuptake inhibitors			
Citalopram (Celexa)	20 mg qd	60 mg qd	$61.58
Escitalopram (Lexapro)	10 mg qd	20 mg qd	$65.28
Fluoxetine (Prozac)	20 mg qd	80 mg qd	$81.78
Fluoxetine (generic)	20 mg qd	80 mg qd	$61.80
Fluoxetine (Prozac Weekly)	90 mg qwk		$71.04
Fluvoxamine (Luvox)	50 mg qd	150 mg bid	$59.70
Paroxetine (Paxil)	20 mg qd	60 mg qd	$70.98
Paroxetine (Paxil CR)	25 mg qd	75 mg qd	$75.86
Sertraline (Zoloft)	50 mg qd	200 mg qd	$65.24
Tricyclic antidepressants			
Amitriptyline (Elavil, Endep, Vanatrip)	100 mg qhs	300 mg qhs	$ 7.99
Desipramine (Norpramin)	100 mg qhs	200 mg qhs	$18.54
Doxepin (Adapin, Sinequan)	100 mg qhs	300 mg qhs	$8.12
Imipramine (Tofranil)	100 mg qhs	300 mg qhs	$31.96
Nortriptyline (Aventil, Pamelor)	75 mg qhs	150 mg qhs	$ 8.71
Others			
Bupropion (Wellbutrin)	100 mg tid	150 mg tid	$92.33
Bupropion (generic)	100 mg tid	150 mg tid	$64.62
Bupropion (Wellbutrin SR)	150 mg bid	200 mg bid	$87.09
Mirtazapine (Remeron)	30 mg qhs	45 mg qhs	$80.79
Nefazodone (Serzone)	100 mg bid	300 mg bid	$74.94
Trazodone (Desyrel)	100 mg bid	300 mg bid	$15.98
Venlafaxine (Effexor)	37.5 mg bid	150 mg tid	$74.39
Venlafaxine (Effexor XL)	75 mg qd	225 mg qd	$66.25
Lithium (Eskalith, Lithobid, Lithonate, Lithotabs)	300 mg bid	600 mg bid	$13.70

*Costs from www.drugstore.com, November 2002.

- Preexisting heart disease and increased suicide risk are both relative contraindications to TCAs.[8]

Helping nonresponders

Patients whose symptoms do not improve with therapy could be switched to a different monotherapy or to multiple drugs. Drug choices for treatment-refractory and nonresponding patients have evolved more by anecdote than by systematic study.[9]

Switch drugs. The benefit of switching patients to another category of antidepressant was recently demonstrated in a study where nearly half of patients who did not respond to an initial antidepressant, whether SSRI or TCA, responded when switched to the alternate agent (SOR: **A**).[38] It is also beneficial to switch medications within a category (SOR: **B**).[27,39,40]

Add a drug. Adding a second antidepressant from a category with a different mechanism of action often enhances clinical efficacy. This has been demonstrated in combining an SSRI with a TCA (SOR: **B**).[41] Though response rates are very similar for various antidepressants, complete remission and rates of response in severely depressed patients may be higher in dual-action antidepressants (SOR: **A**).[34,35,36]

Add lithium. A great deal of evidence supports the use of lithium augmentation (SOR: **A**).[42,43] This agent should be used more in primary care and not only by psychiatrists. A recent meta-analysis of double-blind, placebo-controlled studies of lithium (given at a dosage of at least 800 mg/d or at a level high enough to achieve a serum drug concentration of ≥0.5 mEq/L for at least 2 weeks) found a summary pooled odds ratio of response to lithium of 3.31 (95% CI, 1.46–7.53) with a NNT of 3.7.[44] Other studies have been less clear on the optimal dose or blood level, so a starting dose of 300 mg twice daily with a serum drug concentration of 0.4 mEq/L has been recommended.

If renal function is normal, the concentration of lithium can be checked 5 days after a patient has received a stable dosage, at least 8 hours following the last dose. Lithium may cause thyroid abnormalities; monitoring should include a measurement of thyroid-stimulating hormone, repeated at 6 months and 1 year.

Other augmentation options. Augmentation of antidepressants with buspirone has been proven useful in major depression (SOR: **B**).[45] Thyroid supplementation may also increase the effectiveness of antidepressant therapy using triiodothyronine (T_3), at doses not to exceed 50 mcg per day (SOR: **B**).[46,47] Electroconvulsive therapy (ECT) has a high rate of therapeutic success, including speed and safety, but it is not administered as first-line treatment by psychiatrists except in severe cases (SOR: **A**).[48,49] Augmentation with antipsychotic or anticonvulsants is another strategy that shows some benefit for select patients.[50]

Texas Medication Algorithm Project

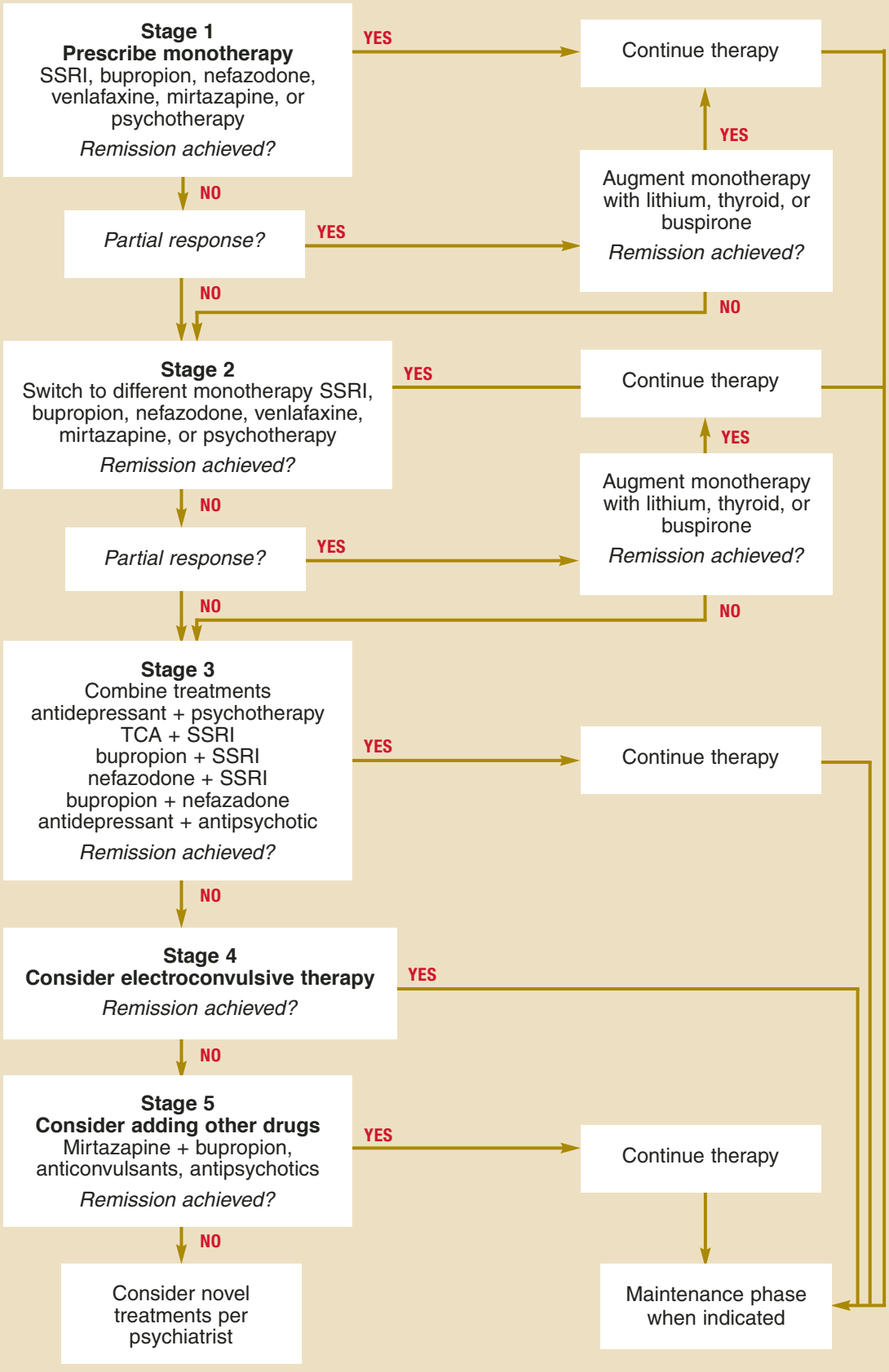
The process of drug selection just described can avoid treatment-threatening side effects, enable patient adherence to treatment, and maximize the potential for therapeutic response. However, the model can become disorienting for the clinician and the patient if 1 or 2 initial selections for treatment do not succeed. A useful synergy may be achieved by adapting the intuitive model to an algorithmic model—the Texas Medication Algorithm Project (TMAP). TMAP is an evolving model that reflects ongoing clinical research in the treatment of depression.[27]

Developed in 1995 from a review of existing antidepressant research and several consensus conferences, the TMAP (continually updated with new research findings) has developed algorithms for treatment of schizophrenia and bipolar disorder in addition to major depression. At each stage in the depression algorithm, treatment plans similar in efficacy and safety are grouped together, and the clinician is given a limited number of options. The later stages in the algorithm are more complex, admittedly with a greater potential for medical complications (**Figure**).[51]

The algorithm represents a tentative foundation for a sequenced medication plan. Research

FIGURE

Treatment of chronic major depression*



*Modified from the Texas Medication Algorithm Project

pertaining to the selection of antidepressant medication is underway, sponsored by the National Institute of Mental Health. Unlike most antidepressant trials, this study includes subjects with significant concomitant medical illnesses.

When to refer

Patients requiring referral to a psychiatrist include those with suicidal ideation or severe depression, aggressive ideation, bipolar disorder, atypical depression, psychotic depression, substance abuse, or treatment resistance.[52] Referral to a licensed counselor should be offered to most patients with depression, with or without psychiatric involvement, though many factors (eg, patient motivation, capacity for insight, patient perceptions of therapist) will affect follow-through and outcome.

MAINTENANCE THERAPY

Once full remission has been achieved, 6 to 12 months of continued pharmacotherapy at the same dose is recommended, as it decreases the risk of relapse by 70%.[5,21,26] More than half of patients will have a recurrence of depression in their lifetime, and they should be advised about this risk.[1]

A second episode of major depression confers an 80% chance of additional recurrences, and patients should therefore be maintained on medication for 1 to 2 years.

A third episode requires indefinite maintenance treatment because of a 90% recurrence rate.[3,26]

Follow-up visits after remission can be tapered gradually to once every 3 months. Discontinuation of therapy should be done gradually to minimize withdrawal reactions; it also necessitates follow-up visits or phone calls.

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