# Algorithm for the Treatment of Chronic Depression

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Chronic depression, which is marked by a course of illness lasting 2 years or more, encompasses 4 subtypes of depressive illness: (1) chronic major depressive disorder, (2) dysthymic disorder, (3) dysthymic disorder with major depressive disorder ("double depression"), and (4) major depressive disorder with poor interepisodic recovery (i.e., in incomplete remission). In the 1990s, chronic depression had a reported prevalence rate of 3% to 5% and accounted for 30% to 35% of all cases of depression in the United States. The authors present an algorithm modified from the Texas Medication Algorithm Project for patients with chronic depression. This treatment algorithm recommends a progression of steps or stages in treating chronic depression. The first stage is monotherapy with the selective serotonin reuptake inhibitors, nefazodone, bupropion sustained release, venlafaxine extended release, mirtazapine, or psychotherapy. Later options include combination therapy, electroconvulsive therapy, atypical antipsychotics, and novel treatments. Utilization of a comprehensive treatment algorithm for chronic major depression should encourage efficient, efficacious treatment.

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Now recognized as a serious and often chronic illness requiring long-term treatment, major depressive disorder (MDD) has a significant negative impact on the productivity and well-being of those affected. It is estimated that 10% of the U.S. population will experience depression annually and that 17% will become depressed at some point during their lifetime.[1]

Although effective treatments are available, extensive documentation demonstrates that MDD is often underrecognized and undertreated. Only one third to one half of individuals with MDD are properly recognized by practitioners.[2–4] Of those who are recognized, many do not receive adequate treatment. There is a wealth of evidence suggesting that over 50% of patients with major depressive disorder are not prescribed an adequate dose of antidepressants or treated long enough to achieve optimal benefit.[5–8] This is unfortunate because when treated adequately, depressive symptoms usually respond well to antidepressant medications.

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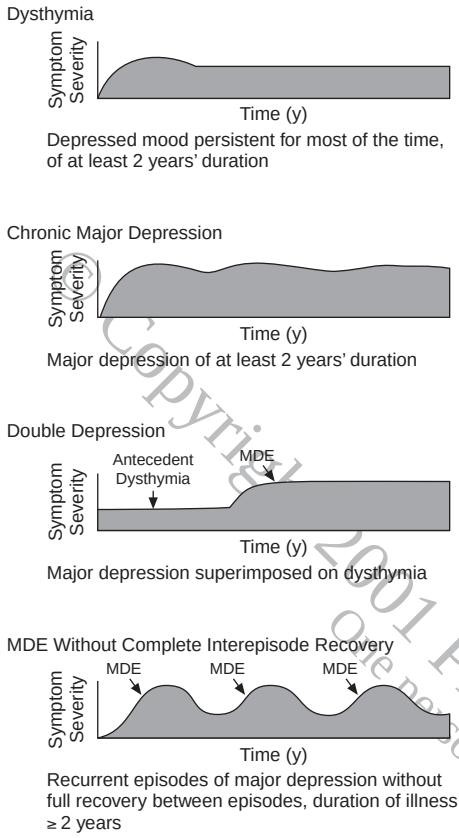
*Chronic depression*, as opposed to acute episodic MDD, refers to depression that is marked by a course lasting 2 or more years. This form of depression is generally associated with poorer outcomes than depression that does not follow a chronic course. Additionally, the coexistence of other psychiatric illnesses (anxiety disorders, personality disorders, and substance abuse) with chronic depression frequently results in poor clinical outcomes.[9] The significant prevalence of chronic depression, as well as the level of associated dysfunction, warrants specific emphasis for this subgroup of patients with MDD.

## SUBTYPES OF CHRONIC DEPRESSION

Chronic depression encompasses 4 subtypes of depressive illness: (1) chronic major depressive disorder, (2) dysthymic disorder, (3) dysthymic disorder with major depressive disorder ("double depression"), and (4) major depressive disorder in incomplete remission.[1] Figure 1[10] provides a graphic example of how these clinical presentations may appear.

Chronic major depressive disorder is defined as major depression that lasts at least 2 years. On the other hand, dysthymic disorder, or dysthymia, is characterized by a lower-level depressed mood that is present the majority of the time for 2 years or more. Those who suffer from double depression experience a major depressive episode within the context of dysthymia. Typically, these patients have the worst prognosis when compared with the 3 other subtypes of chronic depression.[11] Major depressive disorder in incomplete remission is characterized by recurrent

**Figure 1. Clinical Presentations of Chronic Depression**[a]




[a]Adapted from Keller et al.,[10] with permission. Abbreviation: MDE = major depressive episode.

episodes of major depression without full recovery between episodes.[1] It is estimated that 25% of patients with acute MDD have a preexisting dysthymia. Furthermore, 20% of patients with acute MDD may not recover in 2 years, whereas 12% of those patients may not recover in 5 years.[12]

## PREDICTORS OF CHRONIC DEPRESSION

In the 1990s, chronic depression had a reported prevalence rate of 3% to 5% in the United States and accounted for 30% to 35% of all cases of depression.[1] Certain populations tend to be more vulnerable to chronic depression than others. These include patients with both dysthymic and major depressive disorders, those whose depression had an early onset, and those with comorbid medical illnesses, anxiety disorders, and histories of substance abuse.[9] The chronicity of the disorder is affected by the individual's prior clinical history, a history of dysthymia, comorbidity, and characteristics of the current depressive episode.

Early onset of a depressive disorder plays a significant role in chronic depression. It has been shown that initial onset of depression in childhood or adolescence is often associated with longer and more severe depressive episodes, with higher rates of recurrence and more functional impairment among these individuals compared with those who experience a depressive disorder after the age of 21 years.[13] Moreover, lifetime substance abuse and comorbid personality disorders are more common with early-onset depressive disorders.

## PATIENT FUNCTIONING AND QUALITY OF LIFE

The annual cost of depression in the United States is approximately $43 billion, with 72% of that amount attributed to indirect costs due to functional impairment.[14] This impairment includes reduced productivity at work or school, often resulting in unemployment, underemployment, or total disability. Chronic depression takes an immense toll on an individual's overall quality of life as well. This may not only be reflected in a reduction in work performance, but also a loss of enthusiasm and pleasure in outside activities or friends. Individuals with chronic depression may struggle to maintain relationships and/or perform in their role as parent or spouse.[14]

Functional impairment is even more evident in those patients with an early onset of the illness. Depressive symptoms occurring at a crucial developmental period may result in a significant reduction in the amount of education attained, which in turn may affect future employability and potential earnings.[15] Basic levels of functioning may be achieved, but development of complex behaviors such as are required in the workplace and in intimate relationships may be stunted or arrested.[16]

Early detection and treatment of depressive disorders is crucial to ensure optimal benefit.[15] The failure to return to normal levels of social functioning after a depressive episode appears to correlate with the age at onset.[17] A positive response to medication may be predicted by the patient's baseline quality of life, with those who are married and more educated most likely to respond.[18] Other factors affecting the attainment of remission include stress levels before and during the recovery period, the amount of delay between symptom onset and active treatment, adverse life events, and family history.[19] Proactive treatment of depression is essential to complete remission and recovery.

## VULNERABILITY TO RELAPSE AND RECURRENCE

An issue of critical concern to clinicians treating depression is the high incidence of relapse and recurrence following an acute episode. The most cited predictor of poor long-term outcome is incomplete remission of depressive symptoms.[20] Even after 6 months of active treatment, up to 50% of those treated for depression do not

fully recover.[20] One 12-month follow-up study[21] reported a 37.1% relapse rate for depression in primary care settings, with major risk factors for relapse being persistent subthreshold symptoms 7 months after initiation of antidepressants as well as a history of multiple depressive episodes or chronic mood symptoms for 2 years.

Once recovery is achieved, the risk of recurrence of depression is 40% or more during the first 2 years, and more than 80% over a 15-year period. People who experience 1 episode of depression have a 50% chance that the illness will recur, increasing to 70% with 2 episodes and 90% with 3 episodes.[22]

In one 10-year longitudinal study,[23] nearly two thirds of subjects had a recurrence of major depression. The number of lifetime depressive episodes significantly increased the probability of recurrence by 16% with each successive episode. However, evidence also shows that the relapse rate decreased as the periods of recovery or wellness increased, suggesting the importance of adequate treatment.

## RESIDUAL SYMPTOMS AS AN INDICATOR OF RELAPSE OR RECURRENCE

Recovery from a major depressive episode (MDE) with residual subthreshold symptoms appears to be a strong clinical marker for rapid or frequent relapse.[24] Patients with persistent subthreshold symptoms following recovery have been found to have a recurrence 3 times faster[25] and relapse 5 times faster than asymptomatic patients.[24] Recurrence of any depressive episode (dysthymia, minor depression, MDE) was 12 times quicker in recovered patients with subthreshold symptoms. Thirty-four percent of asymptomatic patients remained symptom-free during follow-up compared with 7.7% of patients with subthreshold symptoms. Well intervals were 7 times shorter for patients with residual symptoms, and those patients had more chronic depressive episodes.

Overall, researchers have shown that individuals who experience residual or subthreshold depressive symptoms on recovery from an MDE have a significantly more severe and chronic course of illness, significantly more frequent and chronic MDEs, shorter periods of wellness, and fewer asymptomatic weeks.[24] Complete remission of depressive symptoms during active treatment appears to be essential to a positive long-term outcome.

## TREATMENT OF CHRONIC DEPRESSION

Effective treatment of depression consists of 3 basic phases. The acute phase occurs during the first 6 to 12 weeks of treatment and is the phase in which the depression is actively treated. As the depressive symptoms remit, patients enter the continuation phase, and they remain in this stage until approximately 12 months have passed since the initial treatment. This is the phase in which relapse prevention is most important. The maintenance phase begins approximately 1 year after treatment was initiated and may last as long as a lifetime. The goal of this phase is to prevent recurrence of depression. Planning for all phases of treatment should include patient education, long-term planning, and the selection of appropriate treatments. Ultimately, the goal of treatment is to achieve the full remission of the patient's symptoms and to restore psychosocial functioning.[26]

Depression is a highly treatable illness. The available therapeutic options are successful in 60% to 80% of all patients, so patients who receive treatment have a good chance of achieving remission. In treating MDD, health care providers must strive to not only achieve full symptomatic remission, but also to improve the quality of life and to prevent relapse and recurrence.[26] Treatment of MDD often consists of antidepressant therapy or psychotherapy, with new evidence indicating that patients who receive both forms of treatment may have the best prognosis. The effectiveness of any treatment, however, depends largely on the clinician's ability to make an accurate diagnosis, prescribe effective dosing (when antidepressants are indicated), and maintain appropriate follow-up.

### Efficacy of Medication

Antidepressants have been proved to be effective in the treatment of chronic depression during the acute, continuation, and maintenance phases. In choosing the best antidepressant for a patient, health care providers must consider many factors: the patient's past response to similar drugs, medication interactions, short- and long-term effects, patient preference, likelihood of adherence, comorbidity (medical or psychiatric), and cost.[26] For example, if the patient also suffers from a chronic medical illness such as myocardial infarction, diabetes, or stroke, clinicians must give careful consideration to the impact that an antidepressant may have on both illnesses. Another challenge that clinicians face in treating chronic depression is that of finding a drug that is effective in both the acute and long-term phases of treatment. A drug that provides relief of symptoms in the acute phase only is not recommended because it does nothing to treat the chronic nature of the illness.

Finally, choosing a medication that a patient can tolerate is essential to the success of treatment. Therefore, when selecting a medication, the clinician should take into consideration its side effect profile. Maintenance therapy requires the patient to remain on the same dosage that was effective in the acute phase. Additionally, medications that are well tolerated are associated with higher rates of adherence, so it is critical for this medication to be tolerable to the patient.

Recent clinical trials have shown several medications to be efficacious in the treatment of chronic depression. With varying mechanisms of action, they include, among others, imipramine, sertraline, desipramine, and nefazo-

done. Thase et al.[27] compared sertraline with imipramine in the treatment of dysthymia. Full response was achieved by 47% of those treated with sertraline compared with 39% of patients taking imipramine. Not only did subjects taking sertraline show greater rates of full response, but there were fewer dropouts due to adverse events. In another study, Kocsis et al.[28] found both sertraline and imipramine to produce significant treatment effects compared with placebo.

In the Cornell long-term study of chronic depression,[29] patients were given desipramine for acute and continuation treatment and then randomly assigned to either desipramine or placebo in the 2-year maintenance phase. At the end of the 2 years, patients maintained on desipramine treatment were significantly less likely to relapse than those taking placebo.

In a large multisite chronic major and double depression study,[30] patients were randomly assigned to either imipramine or sertraline in the 12-week acute phase. Responders were maintained on treatment with their assigned medication while nonresponders switched medications for the continuation phase. During the 78-week maintenance phase, patients taking imipramine were continued on treatment with that medication while those on sertraline were randomly assigned to either sertraline or placebo. Over the course of the acute and crossover phases of the study, 228 had full response, 158 had a satisfactory response, and 77 were nonresponders. Of those achieving full treatment response, 67% maintained full response and 18% had a satisfactory response during the continuation phase. Of the 158 who had a satisfactory response initially, 47% achieved full response and 33% maintained a satisfactory response during the continuation phase. This finding suggests that extending the time of active treatment may promote full remission of symptoms.

Of those completing the acute phase, the total response rate for sertraline was 52%, while 51% responded to treatment with imipramine.[30] Both medications produced complete symptom remission in about 40% of those completing the acute phase. Sixty-seven percent of full responders taking sertraline were able to remain symptom-free, and 71% of those taking imipramine sustained full response. Of the partial responders, 43% of those taking sertraline achieved full response during the continuation phase, whereas 41% of those taking imipramine became free of symptoms.[31] For both medications, fewer than 20% of full responders had a recurrence of symptoms. In addition, sertraline led to a significant drop in recurrence of depression compared with placebo.[30]

Although the goal of maintenance phase treatment is to prevent recurrence of depression, maintaining an adequate dose of an efficacious medication does not always prevent the recurrence of depressive symptoms. Fortunately, this rarely results in total loss of response to the antidepressant. It is not known why this phenomenon occurs, but it is important to note that recurrence of symptoms does not always indicate loss of efficacy.

Symptoms may reappear because of psychosocial stressors, substance abuse, drug interactions, or various other life changes experienced by the patient. In the cases in which efficacy is truly lost in the maintenance phase, clinicians have a few options that may prevent complete recurrence: increase or decrease the patient's current dose, switch medications within the class or across classes, augment the medication, combine antidepressants, or add psychotherapy. It has been shown that patients who do not respond to an initial medication trial have a 60% chance of response to a second trial of a dissimilar antidepressant.[32]

### Efficacy of Psychotherapy

Whereas psychotherapy and antidepressants have been extensively studied as treatment options for major depression, until recently no large, systematic, controlled clinical trials have examined the use of psychotherapy for chronic depression.[33] However, there is now clear indication that a combination of pharmacotherapy and psychotherapy may be the best treatment option for patients with chronic depression.[34,35]

In fact, findings of a recent study[35] of 680 depressed patients reported that treatment which combines the antidepressant nefazodone with the Cognitive Behavioral Analysis System of Psychotherapy (CBASP) provides greater efficacy than does monotherapy. Nefazodone monotherapy provided quicker results initially and was more efficacious than CBASP alone during the first 4 weeks. By the end of the 12-week acute phase, nefazodone and CBASP monotherapy proved to be equally effective with a response rate of 52% in the CBASP patients and 55% in the nefazodone patients, comparable to results found in studies examining sertraline, imipramine, and desipramine in the treatment of chronic depression.[29,30] However, patients who received both medication and psychotherapy had a response rate of 85%.[35] It has been hypothesized that combined treatments produce a complementary effect because of the immediate impact associated with antidepressants and the delayed impact associated with psychotherapy.

### Treatment of Residual Symptoms

There are indications that the addition of cognitive-behavior therapy (CBT) following successful psychopharmaceutical treatment may significantly decrease residual symptoms, thereby reducing risk of relapse.[36] CBT has been shown to decrease overall illness severity and psychological factors such as guilt, hopelessness, and self-esteem as well as improve social functioning in patients with residual symptoms of depression.[37] Paykel et al.[38] found that in a 17-month maintenance study, CBT significantly impacted relapse rates. Despite ongoing antidepressant treatment, 47% of patients who were tracked relapsed. With the addition of CBT, the relapse rate dropped to 29%.

### Patient Education

Patient education is another essential component of the treatment of chronic depression. Long-term antidepressant maintenance therapy is necessary to protect patients from future depressive episodes. Unfortunately, it is estimated that half of all patients who recover from depression do not receive preventive treatment and are not informed of its importance. There is a tendency for patients to discontinue their medication when symptoms begin to remit; therefore, it is crucial that patients are educated about the need for long-term therapy at the outset of their treatment. Moreover, educating patients about the side effects associated with antidepressant therapy may also improve adherence. The most common adverse events associated with antidepressant medications include sleep disturbance, weight gain, and sexual dysfunction. If a patient is aware of the possible side effects, he or she is less likely to discontinue treatment if an adverse event does occur.

### Treatment and Psychosocial Function

Several studies have shown a number of antidepressant medications to be effective in treating major depressive disorders. In addition to a reduction of symptoms, these medications may lead to improvement in patients' psychosocial functioning and overall quality of life. Again, full remission of symptoms is important to successful treatment and in providing the most benefit to the patient.[14,28] In one study,[14] patients who had only a satisfactory response or nonresponse to medication continued to have impaired functioning levels, whereas those who achieved full remission showed great functional improvement, nearing or matching adjustment levels of controls.

Even after years of social dysfunction, longer-term pharmacotherapy appears to provide significant benefit to patients with dysthymia.[39] Improvement levels were comparable for patients diagnosed with dysthymia and double depression after 6 months of treatment.

## TREATMENT ALGORITHM FOR CHRONIC DEPRESSION (MODIFIED FROM THE TEXAS MEDICATION ALGORITHM PROJECT [TMAP])

Given the managed care environment and rapid advances in medical knowledge, a focused approach to treatment of chronic depression is warranted. Derived from current evidence-based scientific knowledge and expert consensus, treatment algorithms provide a tool to assist clinicians in making treatment decisions.[40,41] Using a step-by-step approach to medication treatment of depression, algorithms simplify treatment decisions. Figure 2 illustrates the progression of stages in treating chronic depression using an evidence-based treatment algorithm. Modifications from TMAP have been recommended for the chronic depression algorithm.

### Treatment Stages

Specific algorithm stages, or steps, each with a range of selected critical decision points (CDPs), recommend a number of therapeutically equivalent strategic options.

Stage 1 medications for the algorithm are the selective serotonin reuptake inhibitors (SSRIs), nefazodone, bupropion sustained release, venlafaxine extended release, and mirtazapine. All of these medications are proven to be efficacious and to promote medication acceptability and compliance due to their minimal side effect profiles.[27,29,30] Table 1 provides an evidence-based dosing schedule for medications utilized in the treatment algorithm. Physicians may choose any of the medications in step 1 on the basis of a patient's past history, current symptoms, and personal preference. In addition, psychotherapy alone may be selected as an option. If a patient shows only partial response to a medication at CDP 3, following an increase in dose at CDP 2, the antidepressant may be augmented with lithium, liothyronine, buspirone, or psychotherapy.

Stage 2 offers tricyclic antidepressants (TCAs) as an option for monotherapy. The later introduction of TCAs is due to a less favorable side effect profile and higher risk of toxicity in overdose. Augmentation also may be used at stage 2 as needed following an adequate trial of antidepressant medication. Stage 2 augmentation could include atypical antipsychotics, as well as the above-mentioned agents, to enhance the patient's response at critical decision points.

Stage 3 utilizes a combination of treatments, including 2 antidepressants (TCA + SSRI, SSRI + bupropion, SSRI + nefazodone, SSRI + mirtazapine, or bupropion + nefazodone), both an antidepressant and an antipsychotic medication (such as an SSRI and olanzapine), or an antidepressant medication and psychotherapy.

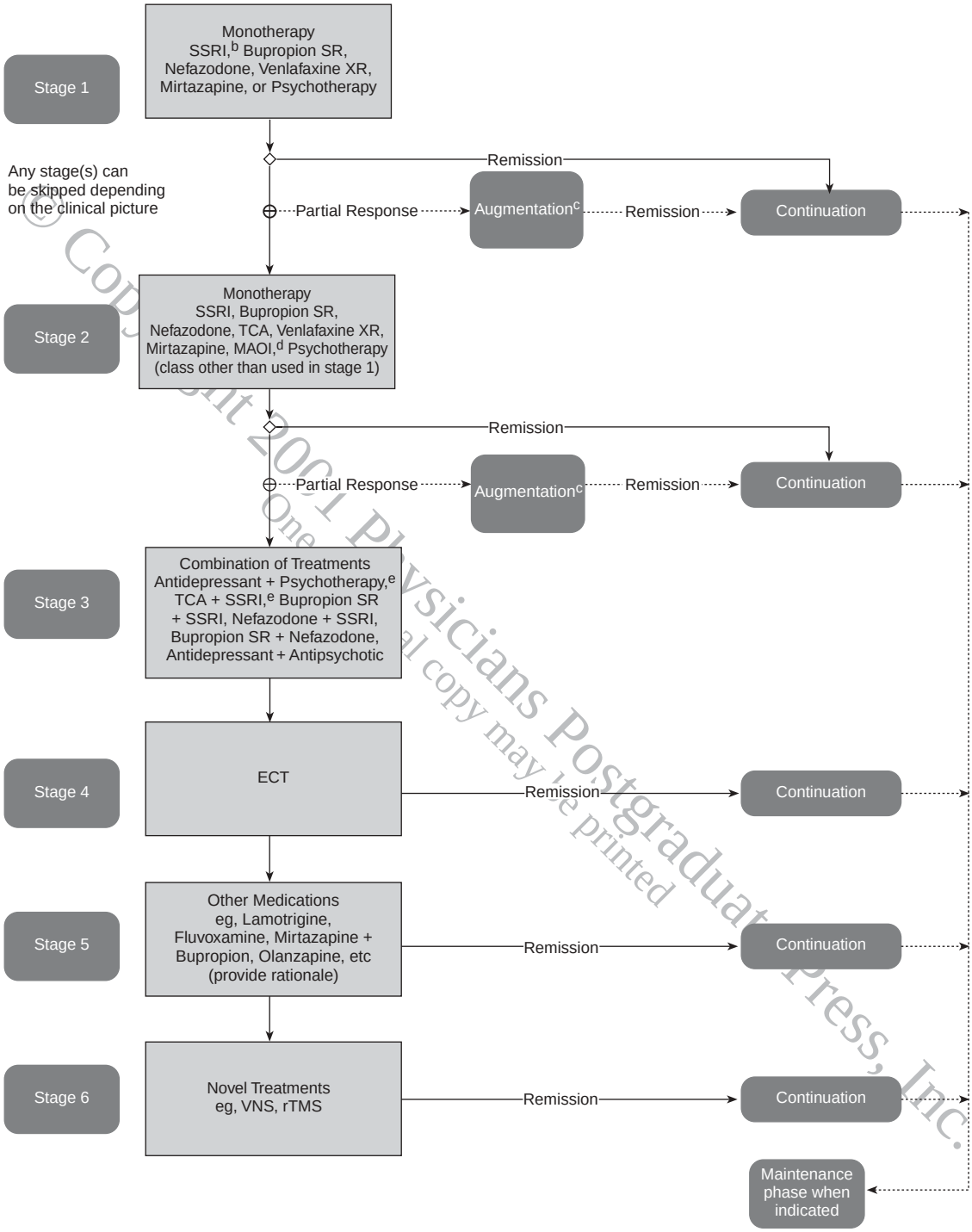
Stage 4 of the algorithm recommends a trial of electroconvulsive therapy if the patient has yet to achieve a full response. This stage, as any other, may be skipped on the basis of clinical judgment and patient choice.

Stage 5 suggests the use of any medication combinations not previously tried.

Finally, stage 6 includes novel treatments, such as vagus nerve stimulation or repetitive transcranial magnetic stimulation.

The design of the chronic depression algorithm is intended to be flexible enough to have a broad applicability for use with different patients, yet also helpful and instructive for the clinician. Only practical and effective recommendations will elicit the desired patient response, which is complete remission of symptoms and a restoration of full functioning. In contrast to the standard TMAP algorithms, the recommendation for chronic depression includes only 2 monotherapy stages to be followed by combination antidepressants in stage 3. Implementation of these recommendations, however, requires further steps in organizing clinical practice design.

**Figure 2. Suggested Algorithm for the Treatment of Chronic Major Depression (modified from the Texas Medication Algorithm Project)[a]**






[a]This material is in the public domain and may be reproduced without permission or cost. Abbreviations: ECT = electroconvulsive therapy, MAOI = Monoamine oxidase inhibitor, rTMS = repetitive transcranial magnetic stimulation, SR = sustained release, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, VNS = vagus nerve stimulation, XR = extended release.
[b]SSRIs include fluoxetine, sertraline, paroxetine, and citalopram.
[c]Lithium, thyroid, buspirone.
[d]Consider TCA or venlafaxine if not tried.
[e]Most studied combinations.

### Critical Decision Points

CDPs have been incorporated to guide physicians in strategies and tactics of medication management. CDPs in this algorithm are set at weeks 0, 4, 6, 8, 10, and 12. Week 0, or CDP 1, is defined as the point at which a new medication regimen is begun. At subsequent CDPs, physicians are asked to make judgments on the basis of the patient's overall improvement and side effect burden. Each CDP gives tactical options such as continuing doses, increasing or decreasing doses, adding an augmenting agent, or moving to the next stage. Patients should be monitored weekly for response and tolerability; however, decisions regarding dosage and medication changes generally are made at weeks 4, 6, 8, 10, and 12.

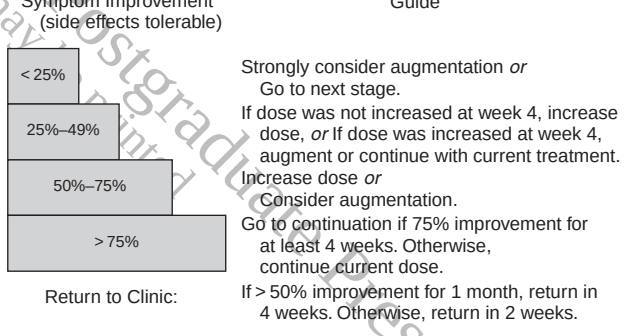
At each CDP, the physician should evaluate the degree of symptom reduction, with the ultimate goal of complete symptom remission. In the event that a patient is slow in showing response to an adequate trial of medication, it may be necessary to extend the duration between CDPs to allow more time for improvement to occur. Treatment of chronic depression may require a medication trial of 12 to 16 weeks to achieve remission. The final decision to make changes to tactics or strategies is always left to the physician's clinical judgment and the patient's preference on the basis of the best treatment for individual outcomes. It is hoped, however, that by including these guidelines physicians will be more likely to make changes to treatment in a more timely manner. An example of how the clinical evaluation of symptom improvement interacts with treatment decisions at a given CDP is shown in Figure 3.

**Table 1. Antidepressant Medication Dosing Schedule[a]**

| Type/ Class | Medication | Initial Target Dose, mg (blood drug level, ng/mL) | Maximum Dose, mg (blood drug level, ng/mL) | Recommended Administration Schedule |
|---|---|---|---|---|
| SSRI | Fluoxetine | 20 | 40–80 | qam |
| | Paroxetine | 20–30 | 40–60 | qam |
| | Sertraline | 50–100 | 150–200 | qam |
| | Citalopram | 20 | 60 | qam |
| TCA | Amitriptyline | 150–200 | 300 | qhs |
| | Clomipramine | 100–150 | 250 | qhs |
| | Desipramine | 150 (> 125) | 300 | qhs |
| | Imipramine | 150 (imipramine + desipramine > 200) | 300 (200–400) | qhs |
| | Nortriptyline | 75–100 (50–150) | 150 (50–150) | qhs |
| Other new generation | Amoxapine | 200–300 | 400 | qhs |
| | Bupropion SR | 200–300 | 400 | bid ≤ 200 mg/dose |
| | Bupropion | 225–300 | 450 | tid ≤ 150 mg/dose |
| | Mirtazapine | 30 | 60 | qhs |
| | Nefazodone | 200–400 | 600 | bid |
| | Venlafaxine | 150–225 | 375 | bid |
| | Venlafaxine XR | 75–150 | 225 | qd |
| MAOI | Phenelzine | 45–60 | 90–120 | qd–tid |
| | Tranylcypromine | 30–40 | 60–80 | qd–tid |

[a]Abbreviations: MAOI = monoamine oxidase inhibitor, SR = sustained release, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, XR = extended release.

**Figure 3. Critical Decision Point Exemplar at Week 6 for Stages 1 and 2 of the Treatment Algorithm for Nonpsychotic Major Depressive Disorder**




## CONCLUSION

Because of its prevalence and detrimental effects, chronic depression continues to be of significant concern to clinicians. Not only does it negatively impact productivity and quality of life, but treatment of chronic depression may be an ongoing battle if certain facts are not recognized. The key to successful treatment includes adequate medication dosing for an appropriate length of time; often, however, we find that such an ideal is not the case in clinical practice. It has been shown that long-term treatment may have a preventive effect on relapse or recurrence. Utilization of a medication algorithm encourages efficient, efficacious treatment of chronic depression.

*Drug names:* amitriptyline (Elavil and others), amoxapine (Asendin and others), bupropion (Wellbutrin), buspirone (BuSpar), citalopram (Celexa), clomipramine (Anafranil and others), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), lamotrigine (Lamictal), liothyronine (Cytomel, Triostat), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), olanzapine (Zyprexa), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), tranylcypromine (Parnate), venlafaxine (Effexor).

*Disclosure of off-label usage:* The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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