A Step Therapy Algorithm for the Treatment and Management of Chronic Depression

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Abstract

Depression is a chronic and progressive condition that, when not treated adequately, can lead to severe morbidity and mortality in patients and increased costs for health plans. Despite the significance of this disease state, the majority of patients are not treated adequately to the widely accepted goal of remission. Patients who do not achieve remission are at greater risk of relapse and recurrence, more chronic depressive episodes, and a shorter duration between depressive episodes. Modeled partially after the Sequenced Treatment Algorithm to Relieve Depression (STAR*D) trial and based on trial data and the consensus statements of a panel of clinical professionals, a step therapy algorithm is proposed in this supplement, including considerations for screening and intervention. The primary concepts in the development of this algorithm were the use of the same clinical tool for both screening and diagnosis and the incorporation of frequent follow-up visits or calls to continuously monitor progress in patients being treated. Also discussed are considerations for drug therapy choices when switching is deemed necessary. Switching to a drug from a different class of agents than the failed trial drug is recommended based on the differential mechanism of action between classes.

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Despite its prevalence in the managed care practice setting, depression remains one of the most underrecognized and undertreated diseases challenging the US healthcare system. Results from the National Comorbidity Survey Replication estimate that no more than 21.6% of patients with major depressive disorder in a given year receive adequate treatment.[1] The chronic nature of depression coupled with the escalating severity seen in patients who are inadequately treated can lead to worsening outcomes and rising costs for both healthcare providers and employers. Further exacerbating these worsening outcomes and rising costs are the frequent comorbidities associated with depression, including anxiety, insomnia, and cardiovascular disease. The situation is even more alarming in patients with treatment-resistant depression (TRD) who continually switch medications, only to experience recurring episodes. With these patients in particular, a logical, stepwise methodology for administering care is imperative, especially one in which there is an evidence-based progression through a series of antidepressant medications coupled with thorough follow-up to ensure that therapy is effectively delivered and received.

Such an algorithm is subsequently described, based on the well-established and accepted treatment goal of remission coupled with newer and more innovative concepts, such as patient support and collaborative care interventions. This algorithm was developed using published trial data along with consensus statements from a panel of well-respected healthcare professionals with significant clinical experience. Not simply a series of sterile step edits in the selection of antidepressant medications, the following step therapy algorithm focuses on the administration of quality care for patients with depression. Therapy delivered in this manner, thoroughly and with a constant focus on outcomes, is the most promising way in which the cycle of TRD can be broken. This level of care is necessary to

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Key Terms

Recurrence:	A regression of patient condition or a return of depressive symptoms. Recurrence is only considered to have occurred after recovery has been achieved during the maintenance phase of antidepressive therapy.[2]
Relapse:	A regression of patient condition to less than optimal physical and psychological status, or, more simply, a return of depressive symptoms. Relapse may occur either before or shortly after remission is achieved.[2]
Remission:	Full restoration of a patient's normal capacity for psychosocial and occupational function, with no residual symptoms. The 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$) uses a score of ≤7 as the threshold for remission; the 9-item Patient Health Questionnaire uses a score of ≤5; and the Quick Inventory of Depressive Symptomology, Self-Report also uses a score of ≤5.[2]
Response:	A significant improvement in depressive symptoms, although residual symptoms may still be present. Response is generally defined as a 50% or greater reduction from baseline score in a number of the standard indexes, including the $HAM\text{-}D_{17}$.[2]
Treatment-resistant depression:	Disease characterized by a failure to respond to at least 2 or 3 antidepressants given at therapeutic doses for more than 4 weeks.[3]

improve quality of life for managed care patients and stem the rising healthcare costs associated with chronic depression.

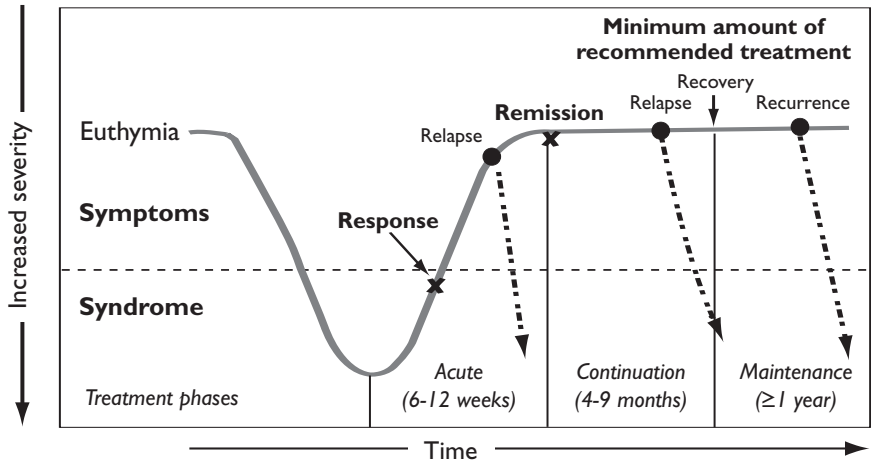
General Treatment Considerations

Usual care for depression is relatively simple at its basest level and typically consists of a prescribed antidepressant, psychotherapy, or both. However, considering the increasingly threatening nature of the disease when not adequately treated, there has been a shift in the treatment paradigm toward more thorough and aggressive therapy. The generally accepted notion for the past several years has been that patients with a depressive disorder should be guided through 3 widely accepted phases of antidepressant medication treatment, culminating in the hallmark end point of antidepressive therapy, remission.[4] Kupfer first introduced the 3-phase model of depression treatment, which represents a thorough and continuous course of pharmacotherapy that mimics the treatment paradigms of many other chronic conditions.[2]

Treatment begins with the acute phase for a patient who has been diagnosed with a major depressive episode (**Figure 1**).[2,4] The primary goal of treatment in the acute phase is to achieve a response through medication or psychotherapy, eventually culminating in remission.[2] First-line medications typically used in the treatment of depression include the selective serotonin reuptake inhibitors (SSRIs), which have reasonable efficacy and a relatively low rate of adverse events. There are a number of agents in this class available as generics. A response is generally identified as significant improvement in depressive symptoms (although residual symptoms may still be present), whereas remission is characterized by full restoration of normal capacity for psychosocial and occupational function (with no residual symptoms).[2] Common depression screening measures quantify this absence of residual symptoms in a similar manner: the 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$) uses a score of ≤7 as the threshold for remission; the 9-item Patient Health Questionnaire (PHQ-9) uses a score of ≤5; and the Quick Inventory of Depressive Symptomology, Self-Report (QIDS-SR) also uses a score of ≤5.

It is recommended that the acute phase of treatment generally last a minimum of 6 to 12 weeks.[2] It is important to note that if a patient's symptoms improve during this phase but do not return to normal functional levels, the course of therapy should be modified toward the aggressive (ie, maximum dos-

Figure 1. Treatment Phases of Depression



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ing of the primary agent) in an attempt to achieve remission.[4] This is true for several reasons including, but not limited to, increased suicide risk, impaired functioning, impaired work productivity, and an increased risk of relapse.[5] Paykel et al found that patients with residual symptoms have a 76% relapse rate compared with a 25% relapse rate for patients who reach remission.[6]

After remission has been achieved and physical and emotional functions have been restored, the continuation phase of treatment begins. At this point in the treatment process, the main goal is to prevent relapse, defined as a regression of patient condition to less than optimal physical and psychological status, or, more simply, a return of depressive symptoms. Relapse may occur before remission is achieved; however, the continuation phase does not begin until remission has been achieved.[2] The minimum recommended duration of treatment in the continuation phase is 4 to 9 months.[2]

The maintenance phase of treatment is essentially long-term management of the depressive disorder. In this phase, treatment is continued with the desired goal of preventing recurrence of a depressive episode. Recurrence, like relapse, is characterized by a regression of patient condition or a return of depressive symptoms. Recurrence, however, is only considered to have occurred after recovery has been achieved. The maintenance phase of treatment may continue indefinitely, depending on an individual's risk of recurrence, but is usually recommended to continue for 12 months for the first episode of depression.

Remission Considerations: Outcomes

Considering the chronic and progressive nature of depression, achieving remission is crucial for predicting future outcomes in the severity of the disease or in the emergence of new depressive episodes. Current data predict a greater than 50% probability that an individual who has had 1 episode of depression will experience a second episode within 5 years. After a second episode of depression, the likelihood of recurrence increases to roughly 70%. The risk of recurrence is greater than 90% after a patient has a third episode of depression.[7-9] Specifically, the risks of not achieving and sustaining remission include a greater risk of relapse or recurrence, more chronic and treatment-resistant depressive episodes, and a shorter duration between depressive episodes.[4] In a 2-year study, Spijker et al observed that longer duration (>12 weeks) of the previous depressive episode reduced the likelihood of recovery by 37%.[10] Analysis of longitudinal data from a primary care sample showed that long-term prognosis (ie, the probability of remission at 6 months and beyond) was strongly related to remission

status at 3 months, with short-term remission being a predictor of long-term remission.[11]

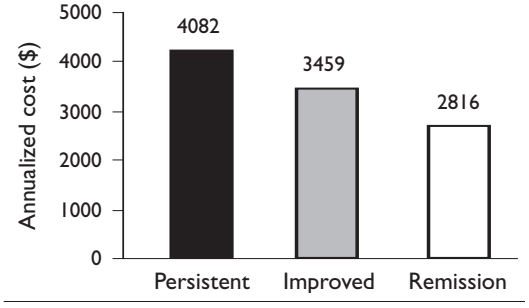
The significance of remission in predicting outcomes in depression is also demonstrable in terms of the existence of residual symptoms in nonremitting patients. In the National Institute of Mental Health's Collaborative Depression Study, patients with residual subthreshold depressive symptoms during recovery (ie, nonremitting) had significantly more severe and chronic future courses of disease than those with no residual symptoms (ie, remitting). Likewise, those with residual symptoms experienced a relapse more than 3 times faster (P <.0001) and had more recurrences, shorter well intervals, and fewer symptom-free weeks during follow-up than asymptomatic patients.[8] In a similar analysis by Judd et al, researchers reported that patients who demonstrated residual symptoms during recovery experienced a relapse more than 3 times faster than patients who were asymptomatic.[12]

Differences in depression severity are also associated with variable outcomes in comorbid conditions. For example, in a study of cardiac patients with depression by Penninx et al, researchers reported that the relative risk of subsequent cardiac mortality was 1.6 (95% confidence interval, 1.0-2.7) for subjects with minor depression compared with 3.0 (95% confidence interval, 1.1-7.8) for those with major depression.[13]

Remission Considerations: Economic

Individuals with recurrent depression tend to utilize more healthcare resources. In an analysis by Greenberg et al, employees with likely TRD used more than twice as many medical services as TRD-unlikely employees.[14] Researchers reported that the average annual cost of TRD-likely employees was $14 490 per employee, whereas the cost for depressed but TRD-unlikely employees was $6665 per employee compared with a cost of $4043 per employee from a random sample of patients without a confirmed diagnosis of depression. Simon et al reported similar results, demonstrating that patients with persistent depression had nearly twice the annual healthcare costs of those who had achieved remission (**Figure 2**).[15]

Figure 2. Annualized Healthcare Cost as Related to Remission Status



Source: Reference 15.

The increasingly frequent and severe episodes of depression observed when remission is not achieved also translate into reduced functioning in the workplace and ultimately have economic implications. Simon et al reported that patients with greater clinical improvement (remitted vs improved, but not remitted or persistent) had fewer missed workdays due to illness (P <.001) and were more likely to maintain paid employment (P = .007).[15] Similarly, Druss et al observed that the odds of missed work due to health problems were twice as high for employees with depressive symptoms over a 2-year period than those without depressive symptoms. Likewise, the odds of decreased effectiveness at work were 7 times higher among patients demonstrating depressive symptoms compared with patients not demonstrating depressive symptoms.[16] The estimated cost of depression in the United States in 2000 was $83 billion per year. Of that, 62% was due to lost work productivity, whereas only 31% was due to direct medical costs.[17]

Switching Antidepressant Therapies

TRD is a chronic and progressive disease state that presents a significant problem for patients and clinicians alike. TRD is characterized by a nonresponse to therapy or a partial response to therapy in which depressive symptoms lessen in severity but still remain. In other words, TRD is characterized by the absence of remission in depressive symptoms despite treatment. The clinical course of TRD can be staged according to treatment history, as proposed

by Thase et al.[18] The 5-stage system is ordered sequentially as follows: stage I, failure of at least 1 adequate trial of 1 major class of antidepressants; stage II, failure of at least 2 adequate trials of at least 2 distinctly different classes of antidepressants; stage III, stage II resistance plus failure of an adequate trial of a tricyclic antidepressant or monoamine oxidase inhibitor; stage IV, stage III resistance plus failure of an adequate trial of a monoamine oxidase inhibitor and tricyclic antidepressant; and stage V, stage IV resistance plus failure of a course of bilateral electroconvulsive therapy. These stages of resistance can also be used as a framework on which a step therapy algorithm can be built, with trials of different treatment options laid out in a stepwise manner.

Outcomes. The positive dose-response relationship observed with antidepressant therapy dictates that the maximum tolerated dose should be used to achieve remission and prevent relapse. If a patient does not demonstrate adequate response with a particular antidepressant after 4 to 6 weeks of therapy at the initial dose or after 2 to 4 additional weeks at the maximum dose, therapy should be adjusted by either treatment substitution using another antidepressant, adding another antidepressant to the current therapy (ie, combination therapy), or adding another compound to the therapy for augmentation.[19] When considering treatment substitution using another antidepressant, it is important to note that the data are inconclusive as to whether an in-class alternative (eg, from one SSRI to another SSRI) is as effective as choosing an agent from another antidepressant class. Instead, it appears as if choosing an antidepressant with a mechanism of action different from that of the failed therapy is likely to be the most successful option (eg, from an SSRI to a serotonin-norepinephrine reuptake inhibitor [SNRI]). Supporting this point, Thase et al conducted a double-blind switch study in patients with chronic major depression who failed to respond to 12 weeks of either sertraline or imipramine therapy.[20] Patients were given the alternate agent (ie, either sertraline or imipramine), and >50% of the nonresponders benefited from the switch, despite the chronicity of their condition.

Economics. Switching antidepressant classes likewise has economic implications that should be taken into consideration when a first-line therapy fails. A claims analysis presented by Kruzikas et al revealed that switching from a failed antidepressant to another agent with a different mechanism of action (ie, from an SSRI to an SNRI or vice versa) resulted in reduced total healthcare costs, regardless of which drug class was attempted first.[21] However, patients who switched from an SSRI to an SNRI experienced a greater average reduction in total costs, from $682 per month to $549 per month (~20%), than those who switched from an SNRI to an SSRI ($663 per month to $631 per month, or ~5%) (**Figure 3**).[21]

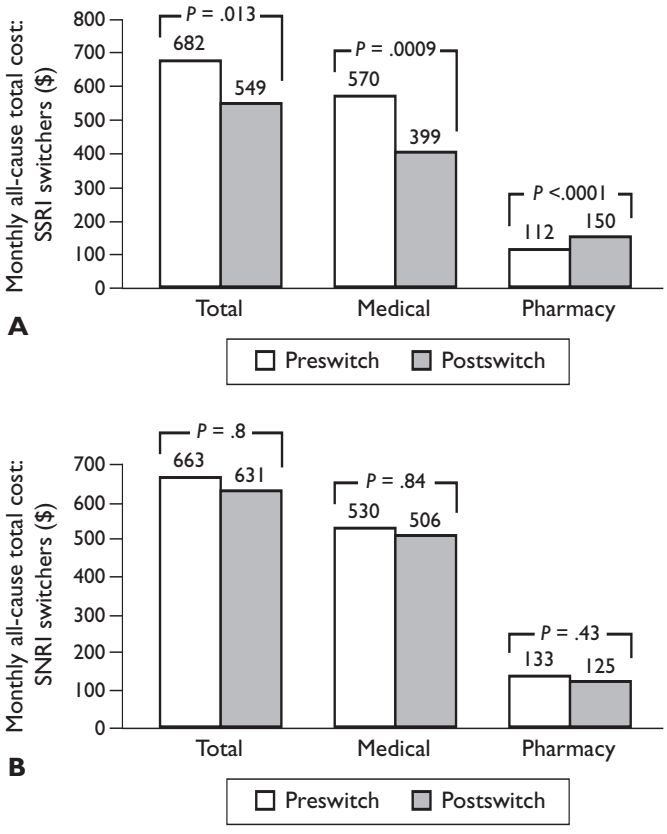
Taking these data into consideration, dual-acting SNRIs present a unique alternative treatment option with proven efficacy and tolerability when the commonly first-line prescribed SSRIs fail in TRD. The alternate mechanism of action of SNRIs may prove beneficial in eliciting a response and achieving remission in patients when agents that primarily affect only 1 neurotransmitter fail.

Step Therapy Algorithm

For an algorithm to serve as a pragmatic means of delivering therapy, it must have several key characteristics. The algorithm should be flexible, adaptable, practical, evidence-based, cost- and outcomes-based, simple, and automated (eg, no prior authorization to hinder care). The 2 main components of the model proposed here are screening and intervention (eg, drug therapy, psychotherapy). Throughout the proposed step therapy algorithm, there should be interventions similar to those used in collaborative care models to improve medication adherence and, ultimately, outcomes as well.

Figure 4 offers a schematic of the medication step therapy algorithm that is presented here for the treatment of depression. As diagrammed, after depression is diagnosed and a patient is prescribed a first-line agent (ie, an SSRI, bupropion, or mirtazapine), the

Figure 3. Reduction in Healthcare Costs Associated with Switching from an SSRI to an SNRI and Switching from an SNRI to an SSRI



SSRI indicates selective serotonin reuptake inhibitor; SNRI, selective norepinephrine reuptake inhibitor.
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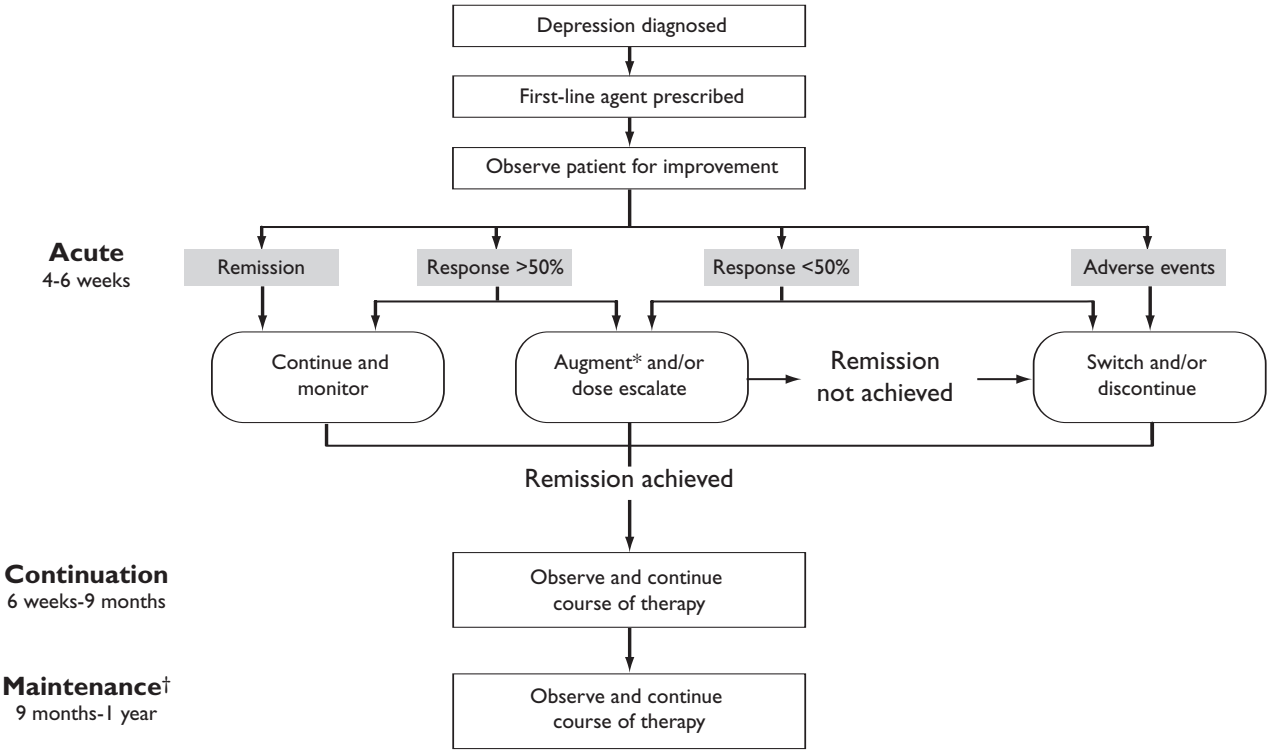
patient is observed for improvement in depressive symptoms during this 4- to 6-week acute phase of therapy. Based on the observed outcome of therapy (ie, remission, response >50%, response <50%, or adverse events) with a particular agent, 1 of 3 courses of action can be taken by the clinician: continuation and monitoring, augmentation and/or dose escalation, or switching and/or discontinuation. Continuation and monitoring are reserved for those patients who either achieve remission or achieve a response >50%. Patients in the latter of these 2 groups are considered to have entered the 6-week to 9-month continuation phase of therapy and can also be tried on the same therapy with dose escalation or augmentation with another drug. However, remission is still the goal of therapy for all patients treated for depression, even those who continue taking their current medication and are monitored, despite a response of only >50%.

In those patients who achieve a response <50%, augmentation and/or dose escalation is again an option, along with switching and/or discontinuation. For patients who experience intolerable adverse events taking the prescribed first-line agent, however, switching and/or discontinuation is the only option, according to the step therapy algorithm mapped out here. After switching and/or discontinuation, the next course of action to be taken by the clinician is again determined by the outcome (ie, remission, response >50%, response <50%, or adverse events) of this modification in therapy. As previously mentioned, remission remains the desired end result of therapy in this algorithm, with observation and continuation of therapy to occur after remission has been achieved. This observation and continuation of therapy extends from the point at which remission is achieved during the continuation phase to anywhere between 9 months and 1 year—the maintenance phase of therapy. A more detailed description of the individual steps of the algorithm follows.

Screening. Certain considerations must be taken into account when developing a screening method for a treatment algorithm. The primary goal in this step is to locate and diagnose the greatest number of targeted patients in an economical manner. Several different criteria by which to screen may be viable for a depression therapy algorithm: screening based on disease history, screening through the employer group (wellness programs), screening based on comorbidities, and screening based on susceptible demographics (eg, women, the elderly). Next, an appropriate screening tool must be chosen. Ideally, the same tool used for screening should be used for tracking outcomes. In the Sequenced Treatment Algorithm to Relieve Depression (STAR*D) trial, the HAM-D_{17} and QIDS-SR were used at baseline, throughout

Figure 4. A Step Therapy Algorithm for the Treatment of Chronic Depression in a Managed Care Setting



*Augmentation can introduce barriers to successful treatment, such as adherence, new adverse events, and financial burdens. If remission is not achieved after 2 trials within the same therapeutic class, the American Psychiatric Association recommends switching to another therapeutic class. A trial of a second agent within the class could be attempted, or a switch to a different class could be made. A maximum of 2 trials in a class is recommended.
†Consider lifetime treatment for patients with recurrent depressive episodes (ie, >3 episodes).

treatment, and at study exit.[22] One must consider, however, that HAM-D_{17} is often considered cumbersome and impractical in the clinical setting other than for research. Also, these scales often do not adequately assess physical symptoms, such as backache, limb pain, and headache, which often cause absenteeism. Other potential screening tools include the PHQ-9, Global Health Questionnaire, Beck Depression Inventory, Zung, Center for Epidemiological Studies Depression Rating Scale, and Two-Question Screen.[23] One additional tool—the PHQ-2, which was developed from the PHQ-9—provides another option featuring both brevity and specificity.[24]

Intervention. Treating the population of patients diagnosed with depression should go beyond simply administering a medication and following up when the prescription runs out. In the STAR*D trial, patients were recommended visits at 2, 4, 6, 9, and 12 weeks to assess symptoms and side effects.[22] Although follow-up intervals as frequent as these may not be necessary to assess response, 4 weeks should be the maximum length of time to pass without follow-up for adult patients. Alternative measures may also be used to collect this crucial information, such as surveys by telephone or Internet (eg, by e-mail or a Web site). As previously mentioned, using the same screening tool and assessment tool would be ideal, and the QIDS-SR (information available at: http://www.ids-qids.org) appears to be the logical choice, because it is self-administered and allows patients to report

progress by phone or e-mail when office visits are not a viable option. Thorough follow-up is necessary to determine whether a given therapy or a particular dosage is effective and tolerable, and it allows clinicians to adjust or switch pharmacotherapy if necessary. A manual was provided to clinicians in the STAR*D trial to provide recommendations on how pharmacotherapy should be adjusted based on patients' responses to the QIDS-C (Clinician Rating) survey.[22]

The first step of the drug therapy component of patient intervention should begin with an SSRI because of the proven efficacy and relatively tolerable side effect profile of SSRIs compared with tricyclic antidepressants, and because many are now available as generics. Tiering should be used to choose a second agent, with agents of differing mechanisms of action being primary choices due to the lack of data demonstrating the benefit of a within-class switch, as previously mentioned.[19,20]

There is much debate on the length of time that can be considered an adequate trial and failure before switching to another therapy in terms of efficacy. Obviously, when adverse events become intolerable, a switch is justified, but lack of desired outcome is more vague. Opinions vary on the length of time to wait for adequate response to therapy, ranging anywhere from 6 weeks to 6 months. As previously mentioned, patients with persistent symptoms in the study by Paykel et al experienced a relapse rate of 76% versus 25% for those who achieved complete remission with no residual symptoms. Ninety-four percent of those in the high-relapse group had persistent physical symptoms.[6] Greco et al found that, with SSRI therapy, painful physical symptom improvement reaches its maximum by week 4.[25] Thus, to avoid a high risk of relapse, mood symptoms as well as physical symptoms must be targeted. Therefore, a strong case can be made for considering 4 weeks an adequate trial for those with associated painful symptoms.

Incentives for adherence are another key component of the drug therapy portion of patient intervention and, when possible, should be administered in the form of vouchers or coupons for reduced copays or other cost savings.

CONCLUSION

Treating depression to remission is a key component of adequate care due to the negative implications of relapse and recurrence in depressive episodes. To provide this adequate care, managed care decision makers must administer care in a logical and evidence-based manner. A step therapy algorithm provides one such manner by which treatment for depression can be delivered to improve patient outcomes and curb escalating healthcare expenditures. This algorithm should feature the same clinical tool for both screening and assessment to keep measures uniform throughout the treatment process. Coupled with frequent follow-up visits or calls to assess progress and tolerability, this will allow clinicians to accurately map patient outcomes and adjust drug therapy appropriately. SSRIs are an acceptable first-line agent for the treatment of uncomplicated depression due to their efficacy, tolerability, and generic status, but when treatment fails, another class of antidepressants should be attempted, particularly in patients with TRD.

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