Treatment-Resistant Depression: Managed Care Considerations

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ABSTRACT

BACKGROUND: Treatment-resistant depression (TRD) presents a unique challenge in managed care, requiring review of both the clinical and economic components of care.

OBJECTIVE: To review the TRD disease state as well as data supporting the various therapeutic options available for the treatment of persistent depression in managed care.

SUMMARY: While there is no consensus on the definition of TRD, persistent disease can generally be defined as depression that fails to respond to adequate treatment. When initial treatment is not effective or tolerable after 6 to 8 weeks of therapy, the American Psychiatric Association (APA) treatment guidelines recommend dose titration, augmentation, or switching. In the case of a therapy switch, the body of evidence suggests that selection of an agent with a different mechanism of action than the initial agent may be the most effective treatment. Furthermore, when patients maintain continuous therapy for the recommended treatment duration, outcomes are improved compared with patients who discontinue therapy early. As a result, the most effective treatment strategies promote improved patient compliance as well as the use of agents associated with a reduced incidence of premature discontinuation and therapy change early in the treatment program. While data supporting these clinically effective components of therapy exist, few data are available demonstrating the most cost-effective therapeutic options for TRD.

CONCLUSION: This analysis suggests that managed care providers could benefit from a model that they can customize to evaluate the overall cost-effectiveness of different strategies in the management of depression.

KEYWORDS: Treatment-resistant, Depression, Economic model, Switch, SSRI, SNRI, Venlafaxine extended release (XR), Managed care, Cost-effectiveness

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Major depressive disorder (MDD) is the second most common psychiatric disorder in the United States.[1] The lifetime prevalence for major depression appears to be between 6% and 16%.[2,3] While the etiology of depression is not fully understood, evidence suggests that depression is the result of a complex interaction among biological, genetic, psychosocial, and environmental factors.[4,5]

The *Diagnostic and Statistical Manual, Fourth Edition, Text Revision* (DSM-IV-TR) outlines common signs and symptoms of a major depressive episode.[6] While not a definitive list, the following signs and symptoms are derived from DSM-IV-TR criteria:

1. Loss of interest, satisfaction, or pleasure in almost all activities, lasting at least 2 weeks
2. Appetite and sleep disturbance (early morning awakening is "classic")
3. Decreased energy, concentration, or libido
4. Low self-esteem or excessive guilt
5. Recurrent thoughts of death or suicide
6. Psychomotor agitation or retardation
7. Occasional psychotic features (delusions, hallucinations)
8. Atypical features may be present in elderly, children/adolescents

The risk of depression may be related to the same combination of factors that produce depression.[5] The highest rates of depression occur in individuals between the ages of 25 and 44 years. Females are almost twice as likely (10%-25%) as males (5%-12%) to experience depression. Genetic predisposition appears to be a significant risk factor. Individuals with first-generation relatives with major depression have a 1.5 to 3 times greater chance of experiencing depression compared with individuals without a similar family history.[4,7] Individuals who have been victims of trauma or abuse are also at increased risk of depression.[8,9] In addition to the risk factors described, some medications can cause depression-like symptoms, including sedatives, narcotics, and pain relievers.[10]

Untreated depression has significant economic, social, physical, and psychological consequences. Several factors contribute to the economic burden of depression, including the prevalence of the disease, treatment rate, and rate and degree of impairment.[11] Studies conducted in 1990 estimated that depressed workers in the United States lost an average of 5.6 productive hours per week. The same studies estimated that depression-related costs of direct treatment, lost earnings, and indirect workplace costs translated into an economic burden of between $44 and $53 billion per year. These estimates did not include labor costs associated with short- and long-term disability.[12,13] Between 1990 and 2000, the total economic burden of depression remained relatively stable. While treatment rates increased substantially over that period, indirect workplace

TABLE 1 FDA-Approved Antidepressants and Their Proposed Mechanisms of Action[17]

Class/Drugs	Proposed Mechanism of Action
Tricyclic antidepressants (TCAs) (e.g, .amitriptyline, nortriptyline, imipramine, desipramine)	Nonselectively inhibits serotonin, dopamine, and norepinephrine reuptake
Monoamine oxidase inhibitors (MAOIs) nonselective (e.g., phenelzine, tranylcypromine, isocarboxazid; selegeline [transdermal delivery system])	Inhibit enzymes (MAO-A, MAO-B) involved in the breakdown of serotonin, norepinephrine, and dopamine
Selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine, paroxetine, fluvoxamine, sertraline, citalopram, escitalopram)	Selectively inhibit serotonin reuptake; have some effects on other neurotransmitters
Norepinephrine and dopamine reuptake inhibitor (e.g., bupropion)	Inhibits norepinephrine and dopamine reuptake
Serotonin antagonist reuptake inhibitors (e.g., trazodone, nefazodone)	Primarily antagonize 5-HT2 receptors; nefazodone also modestly inhibits serotonin, norepinephrine, and dopamine reuptake
Noradrenergic and specific serotonergic agent (e.g., mirtazapine)	Antagonizes alpha2 autoreceptors and heteroreceptors; blocks 5-HT2A/C and 5-HT3 receptors; stimulates 5-HT1 receptors
Serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g., venlafaxine, duloxetine)	Inhibit serotonin and norepinephrine reuptake

FDA = U.S. Food and Drug Administration

costs remained the largest single cost component.[11] The characteristics of depression, including fatigue, reduced concentration, and difficulty performing routine tasks, all contribute to reduced productivity and increased absenteeism.[11]

Patients with depression also have increased medical morbidity and mortality, including higher rates of premature death related to cardiovascular disease and myocardial infarction.[14,15] In addition, 15% of people diagnosed with major depression will commit suicide, and two thirds of all suicides are related to depression.[16]

Treatment Options

Seven different pharmacologic classes of medications can be used to treat depression (Table 1).[17] The primary targets of most major antidepressant drug classes are the neurotransmitters serotonin and norepinephrine. The oldest agents are the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). TCAs inhibit the reuptake of serotonin and norepinephrine. MAOIs block the activity of enzymes (MAO-A, MAO-B) that are involved with the breakdown of serotonin, norepinephrine, and dopamine. Although both TCAs and MAOIs are effective, their use is limited, primarily because of side effects. TCAs are associated with cardiac, anticholinergic, and hypotensive side effects, as well as the potential for severe toxicity with overdose. Oral MAOIs require adherence to dietary restrictions, except for the newer transdermal systems at entry-level dosages. Newer agents are as effective as TCAs and MAOIs but have been shown to be safer and more tolerable.[17]

Among the newer antidepressant agents, selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) have been commonly used. Studies have shown that SSRIs and SNRIs are effective for MDD when patients remain on therapy at the minimum recommended dose and duration of time set forth in clinical practice guidelines (at least 4-9 continuous months).[18-20] Although many antidepressants have similar efficacy as first-line agents, few studies have compared them as second-line treatments following initial treatment failure.[21]

Treatment Issues

In the managed care environment, initial and subsequent treatment efficacy, tolerability, and adherence influence clinical outcomes and pharmacoeconomic aspects of care. In the treatment of depression, outcomes of particular concern that are affected by these factors include rates of response and remission. While a response is defined by a partial improvement in depressive symptoms, remission is characterized by a full recovery from depressive symptoms and a return to normal functioning.[22] Measures of economic burden (probability of paid employment, time lost from work, and total health care costs) correlate significantly to these clinical outcomes.[23] In a study of 290 primary care patients with MDD, patients who achieved remission at 12 months had a 16% higher probability of paid employment and missed 10 fewer days of work per year compared with patients with persistent depression (mean, 16.8 days).[23] At year 2, patients who achieved remission had 49% lower total health care costs compared with those with persistent depression after adjusting for baseline costs and

other covariates.[23] It should be noted, however, that only 1 of the economic endpoints in this study reached statistical significance.

Even when an agent is effective, lack of compliance can be a major barrier to successful treatment. The ability of the patient to tolerate a drug's side effects strongly influences their compliance with therapy. Developing effective pharmacotherapy strategies that improve adherence and increase remission rates can potentially lower costs, reduce the risk of relapse, and improve psychosocial functioning and productivity.[24,25]

Treatment-Resistant Depression

While there is no consensus on the definition of treatment-resistant depression (TRD), certain guidelines based on accepted clinical outcomes measures, such as the Hamilton Rating Scale for Depression (HAM-D), can be used to identify TRD. Importantly, most published definitions of TRD imply that the patient has had either no response or inadequate response to adequate treatment. Nierenberg and DeCecco suggested that TRD in patients who received adequate treatment could be defined based on any of 3 criteria: failure to achieve a minimum response (e.g., less than a 25% decrease from baseline HAM-D score), failure to achieve a response (e.g., less than a 50% decrease from baseline HAM-D score), or failure to achieve remission (e.g., a final HAM-D score of at least 7).[26]

Patients who are treatment resistant use a disproportionately larger share of health care resources, have significantly more claims for comorbid conditions, and cost employers more in lost productivity compared with patients with major depression who respond to treatment.[27]

Many depressed patients fail to achieve a response or remission after being placed on initial therapy with an SSRI. Second-line pharmacologic treatment options include titrating the dose of the initial antidepressant, augmenting therapy with a second agent, or switching to another SSRI or an agent with a different mechanism of action, such as an SNRI.[28-31] The ARGOS study evaluated an SNRI, venlafaxine extended release XR, in patients who had failed to respond to or could not tolerate conventional antidepressants, primarily SSRIs, in a psychiatric outpatient setting. Those treated with venlafaxine XR had significantly higher remission rates (59.3%) at 24 weeks compared with those treated with conventional antidepressants (i.e., paroxetine, citalopram, sertraline, fluoxetine, mirtazapine, or other treatments) (51.5%; $P<0.001$).[21]

Recent results from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study showed that among patients who did not achieve remission with initial therapy, approximately one third achieved remission by augmentation with a second agent and about one fourth achieved remission by switching to a different antidepressant.[32] Current American Psychiatric Association (APA) practice guidelines suggest that if at least moderate improvement is not observed following 6 to 8 weeks of initial pharmacotherapy, the treatment regimen should be reevaluated.[33]

Managed Care Strategies to Improve Depression Treatment Outcomes

When depressed patients maintain continuous therapy for the recommended treatment duration, health care resource costs are reduced compared with patients who discontinue therapy early.[20,34] It then follows that overall costs should decrease when patient compliance is improved and agents associated with a reduced incidence of early discontinuation and therapy change are utilized early in the treatment program.[35] Managed care organizations (MCOs) are challenged to identify optimal, cost-effective strategies for the treatment of depression and improve patient adherence to antidepressant therapy.[36]

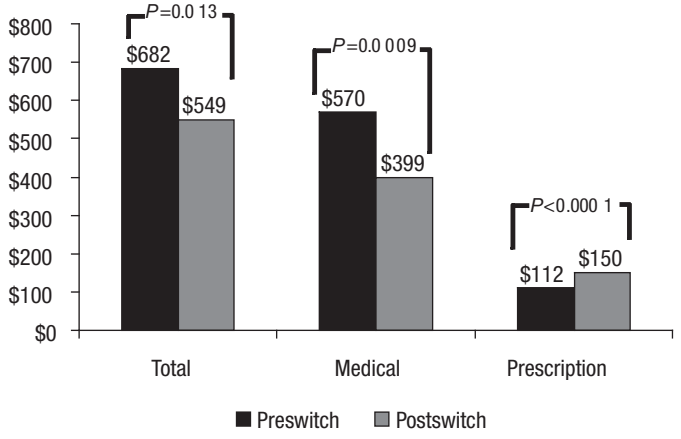
MCOs have a limited role in direct patient care; therefore, they must be creative in developing programs or identifying treatment strategies that have the potential to influence patient adherence. Compared with standard care models, patient support programs (collaborative care model) that educate patients about the value of medication adherence, increase awareness of potential adverse events associated with antidepressant medications, and provide follow-up to ensure continued compliance were found to improve efficacy in the treatment of depression.[37-40] Mail-based educational intervention has also been shown to positively impact patient adherence to therapy.[36]

When initial treatment is not effective or tolerable, APA treatment guidelines recommend that the clinician should consider treatment with another agent. While there is not a solid body of data to guide clinicians in decisions concerning second-line treatment options, the STAR*D trial evaluated 4 levels of treatment in patients who had not responded adequately to an initial standard antidepressant trial: level 1 (identify treatment-resistant patients), level 2 (switch and/or augment antidepressants), level 3 (switch to an agent with a different mechanism of action), and level 4 (treat with either an MAOI or venlafaxine XR plus mirtazapine).[32,41-43] The trial results may help to define which subsequent treatment strategies, in what sequence, and in what combination(s) produce the best clinical results with the least side effects.

Data on switching and related resource utilization in managed care patients are limited. However, some evidence exists that an earlier switch (before 6 weeks of initial treatment) to an agent with an alternative mechanism of action may prevent unnecessary cycling.[44]

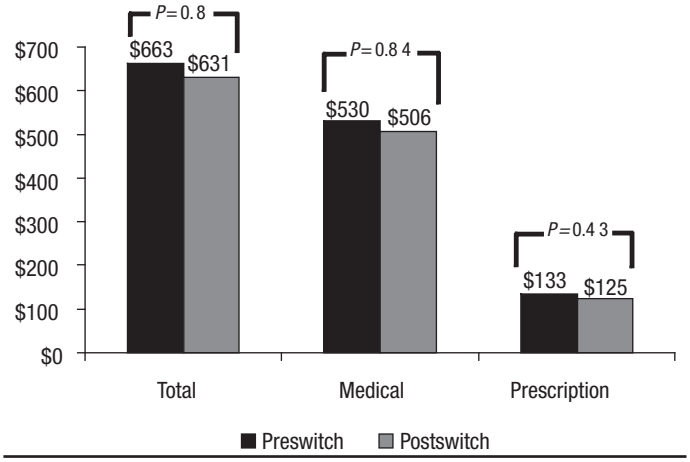
Direct medical costs associated with switching antidepressants were recently reported in a poster presented at the Academy of Managed Care Pharmacy Educational Conference, October 5-8, 2006. Analysis of data from a national database (PharMetrics) of medical and pharmacy claims suggested that, overall, costs declined when patients switched antidepressant

FIGURE 1 Monthly All-Cause Total Costs for Patients Who Started on an SSRI and Switched to an SNRI



SNRI=serotonin and norepinephrine reuptake inhibitors.
SSRI=selective serotonin reuptake inhibitors.

FIGURE 2 Monthly All-Cause Total Costs for Patients Who Started on an SNRI and Switched to an SSRI



SNRI=serotonin and norepinephrine reuptake inhibitors.
SSRI=selective serotonin reuptake inhibitors.

classes. Greater cost reductions due to reduced medical costs were realized when patients switched to an SNRI (venlafaxine) from an SSRI (citalopram, fluoxetine, paroxetine, sertraline) compared with switching to an SSRI from an SNRI (Figures 1 and 2).[44] In addition, higher costs were associated with patients who switched among multiple SSRIs before switching to an SNRI.[44] However, it is important to note that these findings may have been influenced by differences in the baseline characteristics of the patients involved.

Recently, an economic model was developed to explore the results of using generic SSRIs, such as escitalopram, paroxetine controlled release, sertraline, and venlafaxine XR as second-line agents for the treatment of unresolved depression following a treatment failure. Efficacy parameters used to develop the model were derived from clinical trial results based on the HAM-D and Montgomery-Asberg Depression Rating Scale (MADRS).[45,46] While managed care experts express a preference for the self-administered Patient Health Questionnaire. [47] or the Quality Improvement of Depression Scale)[48] as evaluation tools, clinical studies do not use those instruments to evaluate primary endpoints, hence the reliance on HAM-D and MADRS scores in the model.

The economic model, which was constructed in Microsoft Excel, is a budget-impact and decision analysis tool that allows the user to input managed care-specific information. Results of the analyses and a full description of the model are addressed in the next article of this publication.

Conclusion

When patients with depression fail initial therapy, the result is often increased costs to health plans and a poorer quality of life for patients. Because no clear data support the use of one agent over another as second-line therapy in patients with TRD, managed care providers could benefit from a model that they can customize with their own variables, such as acquisition costs and outcome parameters, to evaluate the overall cost-effectiveness of different strategies.

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