Treating Depression: A Focus on Medication Choices From a Clinical and Managed Care Perspective

Proceedings of the Economic Working Group Advisory Board, May 2002

HIGHLIGHTS

• Goals and Challenges of Optimally Treating Depression in a Managed Care Environment

• Establishing the Real Cost of Depression

• The Economic Model in Theory

• The Importance of Adequate Length of Antidepressant Therapy

• The SSRI Therapeutic Effective Dose Model

• ROUNDTABLE DISCUSSION: Assessing the Utility of And Implementing the SSRI Model Within Managed Care Organizations
INTRODUCTORY MESSAGE

NEIL SOLOMON, MD
Senior Associate of The Zitter Group

Achieving the Best Possible Outcomes
For Patients With Depression
In a Financially Responsible Manner

At the economic working group advisory board titled “Establishing the Real Cost of Depression,” held this spring in Miami, faculty and participants learned from each other regarding the key elements driving the clinical and cost outcomes in the treatment of depression.

We heard presentations from the distinguished academicians David V. Sheehan, MD, MBA, Professor of Psychiatry, University of South Florida College of Medicine, and Bernard S. Bloom, PhD, Research Professor, University of Pennsylvania. Dr. Sheehan gave us an overview of the management of depression including the goals of treatment, i.e., what constitutes a successful outcome, as well as the challenges inherent in accurate diagnosis and in keeping patients compliant with medication regimens. He presented prevalence data and commented on the common overlap of depression and anxiety symptoms. Dr. Sheehan discussed the highly comorbid nature of depression, how it affects other illnesses, the importance of therapeutic dose, adequate length of therapy, and how all of these elements of treating depression, in turn, have a significant effect on global system costs.

From Professor Bloom, we heard about the theoretical foundations that must be laid to build an economic model. And, as a group, we discussed the many nuances of accurately measuring cost and determining which costs really matter. The mandate of our working group was the discussion of what defines effective treatment and what the cost implications are for adequate versus less-than-adequate treatment.

To get a perspective on these key issues, we were able to see and work with an economic model developed by Applied Health Outcomes, a health economics and outcomes research consulting firm based in Tampa, Fla. The model — the SSRI Therapeutic Effective Dose Model — allows users to input data from their own plan or organization in order to examine the effects of changes in clinical and economic dimensions regarding the treatment of depression for a defined population. The model enables users to look at clinical and economic ramifications of various medication choices and to evaluate those choices from their own managed care organization’s perspective.

I hope the reader will gain as much from this publication as did we who attended the meeting.
Treating Depression: A Focus on Medication Choices
From a Clinical and Managed Care Perspective
Proceedings of the Economic Working Group
Advisory Board, May 2002, Miami

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Depression is a common, highly comorbid, and frequently chronic condition that is underdiagnosed and undertreated. Its cost ramifications — both direct medical expenditures and indirect costs such as lost productivity — are enormous. Often accompanied by a range of anxiety disorders, depression significantly increases the costs associated with the treatment of other illness such as migraine, back pain, diabetes, and heart failure.

The missed diagnoses and under-treatment of depression have significant economic ramifications, particularly in terms of increasing nonmental health care costs, such as hospitalizations. Accurate diagnosis, appropriate medication treatment — including an adequate length of therapy — and consistent patient compliance with an optimal therapeutic regimen are key to achieving successful outcomes for patients suffering from depression.

An economic working group advisory board meeting titled “Establishing the Real Cost of Depression” — held in Miami, May 4–5, 2002 under direction of The Zitter Group — explored the clinical and economic ramifications of adequate versus inadequate treatment of depression. Central to this dialogue were presentations, discussions, and interactive exercises based on the SSRI Therapeutic Effective Dose Model that allows users to input data from their own health plans or utilize default data to explore the economic and clinical consequences of a wide variety of medication dosing regimens.

Since this working group had gathered to discuss an economic model that focuses on SSRI dosing issues, other important modalities relating to the treatment of depression — such as psychotherapy — were not included on the agenda. The authors recognize the importance of these other modalities but wish to underscore that the primary purpose of the meeting was to explore the ways in which an economic model might inform and aid managed care professionals in making formulary and prescribing-guideline decisions. The articles in this publication are not meant to serve as discourse on the full range of therapeutic options available to clinicians in the treatment of patients with depression.

Physician and pharmacist attendees from managed care organizations across the country participated in the working group as well as a roundtable discussion of the model and other salient discussion points. Excerpts from the roundtable begin on page 21.

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Goals and Challenges of Optimally Treating Depression in a Managed Care Environment

The medical literature is replete with studies that show that depression is managed poorly in today’s health care environment and that failure to diagnose and treat depression properly can lead to serious — yet avoidable — complications. The primary goals and challenges of treating depression involve accurately diagnosing this common, highly comorbid condition and enhancing patient compliance with treatment. Improved patient outcomes, as well as reduced costs and hospitalizations, depend on timely and accurate diagnosis, appropriate use of medications, increased patient and provider education, and enhanced patient compliance. Health care providers and policy makers must also be aware of rates of remission and recovery — the true clinical measures of depression outcomes — and be able to assess the economic consequences of inadequately controlled disease.

Prevalence of Depression

Lifetime and 12-month prevalence rates for major depression in the community are derived from the National Comorbidity Study. These data come from a random sample of the entire U.S. population stratified to be representative of all groups of interest. As in a census study, researchers went out into the community and carefully sampled approximately 8,000 individuals.

Researchers found that the 12-month prevalence rates for anxiety disorders are higher than for major depression (Figure 1). Lifetime rates for aggregate anxiety disorders are 24.9%, with lifetime rates for depression at 17.1% (Kessler 1994).

Symptom Overlap

From the same study published in the Archives of General Psychiatry, we also see just how frequently depression and anxiety symptoms overlap. Anxiety and depressive disorders are highly comorbid conditions. Over 90% of patients have overlapping depressive and anxiety symptoms, particularly fatigue, insomnia, difficulty concentrating, and guilt. In people meeting full syndromal diagnosis for anxiety disorders and full syndromal diagnosis for major depression, there is a 60% overlap on average between major depression and the common anxiety disorders. Therefore, in the majority of cases, when patients present with one disorder, it is likely that they have symptoms of the other.

Jack Gorman, a distinguished researcher from Columbia University, said, “Anxiety and depressive symptoms overlap so frequently that patients with only one disorder may be the exception rather than the rule” (Gorman 1996).

Diagnosing Depression and Anxiety in Primary Care

Overall, detection of depression by primary care physicians (PCPs) is less than optimal. This is due, in part, to the fact that patients don’t always report psychological problems. In fact, among patients suffering from depression, 80% present primarily with physical symptoms. As a result, many of these people either will be misdiagnosed or will not receive adequate treatment for their depression (Kirmayer 1993).

When the PCPs recognize that there is a psychological problem, on average, they marginally overdiagnose

![FIGURE 1 Lifetime and 12-month prevalence of mood and anxiety disorders in the National Comorbidity Survey](chart.png)
anxiety and underdiagnose depression, compared to the true rates for these disorders on the gold standard structured interview (Lecrubier and Hergueta 1998). However, if these are aggregated, it can be seen that the overdetection of anxiety more or less offsets the underdetection of depression to give rates that would be equivalent to those found using a gold standard structured diagnostic interview.

Why is this important? One of the lessons from this study is: “Next time you think you see an anxiety disorder, look again, because it is probably depression.” Clinicians should be concerned, because when PCPs diagnose an anxiety disorder, they often prescribe an anxiolytic. But if the patient really has depression and has been prescribed an anxiolytic, poor outcomes will frequently be the result. Psychiatrists are now saying that the best treatment for anxiety disorders is no longer an anxiolytic but rather an SSRI antidepressant. So, to the extent that physicians use antidepressants to treat all anxiety disorders, adequate use of antidepressants will yield good outcomes for both disorders.

**Successful Outcomes of Treatment**

What is a good outcome? Successful treatment — according to the federal Agency for Health Care Research and Quality — is to reduce symptoms, restore function, reduce relapse and recurrence, achieve and sustain remission, improve clinical status and functionality, and significantly reduce utilization costs.

Unlike many diseases in medicine, psychiatry does not have finely tuned outcome indicators. In medicine, physicians have precise treatment targets, e.g., to get a patient’s blood pressure down to 120/80 mm Hg, or to reduce blood glucose to 70–110 mg/dl. Treatment targets have not been well-established for depression, but researchers doing clinical trials in depression have an important target called remission, which means a ≥70% improvement on a validated instrument, e.g., a score of ≤7 on the Hamilton Depression Rating (HAM-D) Scale.

Why was this particular percentage chosen? One reason is that it represents the patient’s expectations of improvement. Additionally, a ≥70% improvement will have a positive effect on economic outcomes, as well as suicide rates, mortality, and morbidity.

The definition of response is a ≥50% improvement on the HAM-D. Patients who only achieve a response have a 52% likelihood relapsing over the next 12 months. On the other hand, if we look at individuals who have achieved remission, the likelihood of their relapsing over the next 12 months is only about 9%. The difference between 50% and 70% improvement on the HAM-D may seem small, but it is the difference that psychiatrists are aiming for. A 70% improvement is going to protect many more people from relapse in the long run, and small increments in dose make it more likely that people will get to remission (Thase 1992).

These rates of improvement do not represent full recovery, and many clinicians would justifiably state that a 50% improvement in mood score is an unsatisfactory and unsuccessful outcome. It is, however, at this time the standard by which many researchers and clinicians determine efficacy of treatment.

A study published in the *Archives of General Psychiatry* looked at time to response, chronicity of major depression, and impact of severity of illness on recovery and found decreasing rates of recovery over time. After the first six months, rates of recovery declined rapidly, and the longer the patient was ill, the lower the probability of complete recovery.

**Percent of patients who had ≥50% improvement**

<table>
<thead>
<tr>
<th></th>
<th>6 months</th>
<th>2 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>50%</td>
<td>80%</td>
<td>88%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>12%</td>
<td>27%</td>
<td>38%</td>
</tr>
</tbody>
</table>

(Keller 1992).
Simon looked at work productivity and employment status for patients treated to remission. The study found that recovery from depression is associated with fewer missed work days and significant reductions in disability: probability of paid employment was 16% higher among those achieving remission compared with those suffering persistent major depression.

Mean number of work days missed over a two-year period for those with persistent depression was 17, compared with 10 for people classified as responders and six for those who reached remission (Simon 2000). While number of missed work days may not be a perfect proxy for productivity, it does indicate the economic burden placed on employers and health care insurers vis-a-vis the employees with depression who are not adequately treated to remission.

Given an accurate diagnosis and appropriate choice of therapeutic agent, health care providers still cannot achieve remission and recovery without the patient’s compliance, which in the treatment of depression is key.

The Challenge of Patient Compliance

Lin found that approximately 28% of patients stopped taking antidepressants during the first month of therapy, while 44% had stopped their medication by Month 3. Overall, patients who received education and counseling were found to be more compliant than patients who did not.

Among patients who received education and counseling, only severe side effects were associated with discontinuation of therapy. The lesson from this study is that “Physicians may be able to enhance adherence to antidepressant therapy by simple and specific educational messages easily integrated into primary care visits” (Lin 1995).

High dropout rates undermine compliance and reaching optimal treatment outcomes. McCombs reported that of Medi-Cal patients suffering from depression, only 22% were still on an adequate dose of antidepressant medication six months after diagnosis.

When the SSRIs were looked at versus tricyclics (TCAs), compliance with therapy was significantly higher with SSRIs.

The reason for the high dropout rate is adverse events: nearly 60% of patients who discontinued therapy cited adverse events as the reason; 40% gave other reasons, the most important of which was lack of efficacy. In general, in the early phase of treatment, it is mainly adverse side effects driving people out of treatment but later, as patients progress in treatment, side effects become less important, and in the longer run the main reason they stop treatment is lack of efficacy (McCombs 1999).

Premature dropout is a major cause of relapse and recurrence. Patients stopping antidepressant therapy prematurely increase the risk of relapse and recurrence significantly and put themselves at risk for the most serious outcome of undertreated depression and anxiety: suicide (Croghan 1998).

Because general anxiety disorder (GAD) is more commonly associated with suicide than suicide is with moderate depression uncomplicated, or major depressive events complicated by the disorders outlined below, the importance of the choice of treatment and adherence to that regimen in achieving a good outcome is clear. In fact, suicide rates are highest among patients suffering both GAD and depression. In a study published in the Archives of General Psychiatry, the following rates of suicidal ideation were reported.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Risk of suicide</th>
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</thead>
<tbody>
<tr>
<td>Base rate in the general population</td>
<td>2–5%</td>
</tr>
<tr>
<td>Moderate depression uncomplicated</td>
<td>12%</td>
</tr>
<tr>
<td>Major depressive event (MDE) with sleep disturbances</td>
<td>5%</td>
</tr>
<tr>
<td>MDE with fatigue</td>
<td>13%</td>
</tr>
<tr>
<td>MDE with chronic physical illness</td>
<td>27%</td>
</tr>
<tr>
<td>MDE with significant psychosocial problems</td>
<td>31%</td>
</tr>
<tr>
<td>MDE with significant anxiety</td>
<td>63%</td>
</tr>
</tbody>
</table>

(Lepine 1993)

How can we intervene to lower national suicide statistics and health care costs? We must ensure that depression and anxiety are recognized in the primary care setting and that treatment strategies target both disorders.

High Utilization of Medical Resources

Patients who have comorbid anxiety and depression have more severe symptoms and more functional impairment, are twice as likely to use medical services, have a higher number of visits to mental health services, and have a poorer treatment outcome (Lecrubier 2000). However, these high utilizers are not people who typically present to psychiatry: They’re the patients who contribute to the “fat chart” syndrome, so labeled by researchers from the University of Washington Medical School.

Structured diagnostic interviews of these individuals revealed that 70% had a lifetime diagnosis of major depression, 25% panic disorder, 45% GAD, about 25% somatization disorder, and almost 30% alcohol abuse and dependence.

So, a substantial number of overutilizers of general medical care have a psychiatric disorder that has not been properly diagnosed (Katon 1990). The majority suffer from inadequately controlled depression.
Economic Consequences of Inadequately Controlled Depression

Inadequately controlled depression is associated with an almost two times greater use of inpatient, outpatient, and ER health services (Simon 1995). A comparison of hospitalization among depressed and non-depressed patients with the same diagnoses showed that the mean length of stay for depressed patients was 10 days longer than for nondepressed patients (Verbosky 1993).

Salvador-Carulla examined the impact of accurate and timely diagnosis in lowering costs in panic disorder (PD). They looked at costs in four areas in the year before the PD diagnosis compared to the year after: non-psychiatric medical visits, lab tests, hospitalization costs, and lost productivity costs. After diagnosis, global costs were reduced by more than 90%.

The year after diagnosis, the cost of lab tests was reduced by more than 50% compared with the year before diagnosis. Hospitalization costs are small in panic disorder, but they were reduced to zero. The year after the diagnosis, lost productivity costs were 85% lower than the year before diagnosis (Salvador-Carulla 1995).

Conclusion

The challenges of accurate diagnosis reside both in patient hesitancy to report psychological symptoms as well as physicians’ inability to recognize symptoms that have not been clearly communicated. Some physicians may avoid charting a diagnosis of mental illness for reasons of social stigma and/or confidentiality.

In addition, the highly comorbid nature of depression makes it difficult to treat. Patients tend to be non-compliant with therapy, resulting in less-than-optimal clinical outcomes and greater-than-necessary resource utilization.

References

Croghan T, et al. Cost-effectiveness of antidepressant medica-


This is an exploration of the components of the economic burden of depression, depression’s contribution to medical comorbidity and increased resource utilization, the economic consequences of inadequate and untimely treatment, how to determine what an adequate dosing regimen looks like, and a brief examination of the pivotal FDA studies on which the foundations for adequate dosing are built.

**Economic Burden of Depression**

Depression and anxiety disorders exact an enormous toll on the U.S. economy: nearly $44 billion for depression and over $42 billion for anxiety (Greenberg 1993 and 1999).

When I ask residents and many practitioners where they think the costs to treat depression and anxiety are, in the aggregate, most of them say, “Oh, it is from enormous pharmacy costs.” When the data are broken down, however — in this case, for depression — only $1.2 billion of the nearly $44 billion total is attributable to pharmaceuticals (Greenberg 1993) (Figures 1 and 2). The same trend can be seen in the treatment of anxiety. And although pharmacy expenditures are not a major cost center in the overall scheme of things, they obviously are a big concern for managed care.

In fact, managed care is concerned about the cost of antidepressants, because they represent about 14% of the entire pharmacy budget. When you think of all the drugs that are prescribed, antidepressants represent an enormous cost center, and the selective serotonin reuptake inhibitors (SSRIs) make up a large percentage of those prescribed antidepressants. Clearly, as a single class of drugs, SSRIs are a major contributor to the bottom line.

But the cost of medications is only part of the equation. Most managed care decision makers don’t care so much about the cost of the tablet any more. What they care about is the cost per treated patient per month, because that is what they are really paying for.

**Medical Comorbidity and Increased Costs**

So, now that we have a sense of the overall cost, as well as the relative components of the costs of treating depression, we can ask what happens to costs when we add a psychiatric comorbidity to an existing medical condition. From an OCI* data set of almost 230,000 patients, we can see the annual costs for a number of medical disorders with and without depression as a comorbidity. What this translates into is a cost increase of 300 to 500% for treatment of these common medical conditions when the patient has comorbid depression compared to the patient without (Table 1).

**The Effect of Adequate vs. Inadequate Treatment on Costs**

The Revicki paper is a study of 358 primary care patients diagnosed with depression who were seen in clinics of the Group Health Cooperative of Puget Sound, a staff-model HMO. Patients were treated over a three-month period with either recommended doses of an antidepressant or less-than-recommended doses. The study was a secondary analysis of data from a naturalistic, randomized clinical trial. The results of this study, published in the *Journal of Family Practice* in 1998, are critical to the SSRI Therapeutic Dose Model. Revicki calculated total, six-month costs associated with both patient cohorts. Total costs for adequately treated patients were $1,872 versus $2,622 for inadequately treated patients — a $750 difference over the course of the study, or $1,500 annually (1994 dollars). Another interesting point of the study is that baseline and final HAM-D scores were the same for both groups, 14 at the start and 9 at the end of the study. One might then wonder if costs aren’t a more sensitive measure of outcome than the Hamilton scale.

This study is very conservative for a number of reasons. First of all, medications were prescribed for only a

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* OCI is an application service provider that owns the largest private collection of integrated health benefits and risk-management data, and has been providing customized database and reporting applications for more than 15 years.
Other published studies support this same hypothesis that adequate treatment saves money globally. For example, McCombs used Medi-Cal data on 1,648 patients and found nearly a $1,500 annual difference between patients being adequately treated versus inadequately treated. Their definition of adequate used the same AHCPR guidelines; therefore, the doses were very low compared with the doses that we might define as effective in psychiatric practice. But the McCombs group added something that was critical: six months of continuous treatment, and, again, investigators found a $1,500 difference (McCombs 1999).

Finally, a paper in the American Journal of Managed Care explored patterns of antidepressant use in relation to costs. The study examined scenarios of discontinuation, augmentation/switching, upward titration, and partial and full compliance. Again researchers found that patients who were fully compliant and stayed on therapy for three months had the lowest overall costs: $3,393 annually compared with $7,590 for the most expensive switching/augmentation group (Thompson 1996).

**Early Treatment Saves Money**

In another study of late treatment (defined as 15 or more days after diagnosis) and early treatment (14 or fewer days after diagnosis), total costs — medical and psychiatric — were calculated, and, clearly, early intervention did make a difference. Delayed intervention increased costs by 23% (OCI 2001) (Figure 3).

**Adequate Dosing**

If we accept that suboptimal and/ or untimely treatment costs more than adequate, timely dosing, the issue becomes: How can we find evidence on correct dosing and use it as the basis for recommendations to practitioners in a managed care organization? The answer to that question is to go to the pivotal studies that were submitted to the FDA for NDAs or approval of indications for a particular medication. Those are the FDA-audited three-month period. Second, researchers used the AHCPR minimally effective, subtherapeutic dose recommendations, which may or may not be an appropriate standard. (More on this later.) Nonmental health costs were big drivers, especially hospitalizations, which were seven times that of the less-than-adequately treated group. A point that could be made is that given that the doses in this study are so low, even tiny increments of dose can have a substantial effect on cost (Revicki 1998).
and scrutinized studies that yield information on effective dosages that managed care decision makers can reliably use as a basis of prescribing recommendations and guidelines.

**FDA-Approved Studies**

Which study will yield information on the average dose that will produce the best outcomes? The answer is, look at a flexible-dose study. In fact, if you look at any submission to the FDA across a range of flexible-dose studies, you will see that some of them failed to separate out from placebo while others do. When you look to see why, it is often a difference in dosing.

Three pivotal paroxetine studies on generalized anxiety disorder were submitted to the FDA. One was a fixed-dose design, and two were flexible-dose studies. Two of these studies — one fixed and one flexible — separated out from placebo on the LOCF (last-observation carried forward) analysis and were the basis for the FDA’s approval of paroxetine for the GAD indication. (An LOCF analysis includes all patients who were randomized to treatment and who returned for at least one on-treatment visit. Any patient who drops out of treatment or misses a visit has their last observation carried forward. In this way, all patients who took the effective treatment, including dropouts, are included in the final analysis. This is the most conservative and punitive analysis that can be done in a clinical trial. It represents a worst-case analysis.)

The following double-blind, randomized, placebo-controlled study by Pollack utilized a flexible dose that did separate out the effects of paroxetine from placebo. The doses in this study ranged from 20 mg of paroxetine daily to 50 mg, with the mean dose at 26.8 mg (Figure 4). The primary outcome of interest was the mean change from baseline in the total HAM-A score. At week 8, the

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**TABLE 1 Impact of depression: comorbidities**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Annual medical costs per patient without depression</th>
<th>Annual medical costs per patient with depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>$2.56</td>
<td>$6.74</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>$3.27</td>
<td>$8.46</td>
</tr>
<tr>
<td>Asthma</td>
<td>$3.73</td>
<td>$10.56</td>
</tr>
<tr>
<td>Migraine</td>
<td>$3.82</td>
<td>$15.47</td>
</tr>
<tr>
<td>Back pain</td>
<td>$11.61</td>
<td>$33.25</td>
</tr>
<tr>
<td>Diabetes</td>
<td>$13.06</td>
<td>$27.28</td>
</tr>
<tr>
<td>Hypertension</td>
<td>$13.38</td>
<td>$27.16</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>$62.40</td>
<td>$110.94</td>
</tr>
</tbody>
</table>

Actual annual medical costs per patient, based on claims data for 229,776 patients, 1995–1998. 
SOURCE: OCI 2001

**FIGURE 3 Early treatment saves money**

*Delayed treatment of depression (including prescription medication) increases average total costs by 23%*

Actual annual medical costs per patient, based on claims data for 229,776 patients, 1995–1998. 
SOURCE: OCI 2001

**FIGURE 4 Paroxetine flexible-dose GAD study**

HAM-A Item 1 (Anxiety and worry)

Placebo (N=163) 
Paroxetine (mean dose 26.8 mg/day; N=161)

OC dataset. *p<.05 vs placebo. 
SOURCE: Pollack 2001
Finally, to bring this back to our primary focus, it is those pivotal FDA studies that form the scientific underpinnings for the SSRI Therapeutic Effective Dose Model.

References


Conclusion of the study, researchers found a statistically significant decrease in GAD scores among those patients who received paroxetine versus those who received placebo. The bottom line: A significantly greater percentage of paroxetine-treated subjects achieved response or remission by study end, but the dose needed on average to deliver this result was 26.8 mg per day (Pollack 2001). This dose is a more accurate reflection of average effective doses needed in clinical practice than information from a fixed-dose study.

The takeaway here is that consistently, across large numbers of data sets, the data that will guide you about the dose that is going to make the most meaningful improvement on patient outcomes is the average dose at the end of a flexible-dose study that on the LOCF analysis separated out from placebo. Only those mean doses where separation from placebo in the LOCF analysis was achieved will ultimately provide better outcomes than using fixed-dose study guidelines.
We use models — which are simulations of reality — in every aspect of our daily lives. We do this mostly preconsciously, when we want to know where we are now and what the future might hold. Given the information that I have, I can make some predictions about what is going to happen based on current knowledge.

The first thing that a model does is define reality by using a logical or mathematical representation or simulation of that reality. The model pulls together available and important aspects of that reality, and combines this information in some fashion that can simulate the future in a systematic way.

Many think that modeling really began in the 1970s, but in fact, systematic model building began 225 years ago in France. It was invented by the same man who invented one of the first computers, a French mathematician and economist named Francois Quenet. By assembling all of the existing key information about a particular issue and then trying to estimate what was going to happen, he was, in fact, modeling.

Defining Reality to Make Better Decisions

The question then becomes: Why do we use models? The answer is quite simple. Modeling allows us, in a systematic fashion, to calculate a variety of estimates of what is likely to be the current or future status of any given situation. Such an exercise helps us, by using available information, to define reality, and ultimately, to make better decisions.

The economic paradigm is that you cannot have everything, that you have to make choices. This is done in every aspect of our lives. The clothes you wear, the cars you drive, the shoes that you walk around in, are the outcomes of choices made. You have a wide array of options from which to choose; you made clear choices about these goods and services, again mostly preconsciously, based on value — you have traded off quality, desire, need, and money to buy what you want.

Models Weigh Benefits, Risks, and Costs

Economic models can help clinicians, insurers, payers, and other providers — all stakeholders in the health care system — to make the unique decisions that they must make. Payers make one set of, mostly, macro decisions. Practitioners have another set of predominantly clinical choices that they must make. These models help them make choices by enabling them to weigh the benefits and the risks, and then the benefits and the costs. Once you can fairly accurately determine those two outcomes, then you are well on your way to making a decision. It does not necessarily mean that you are always going to choose the highest benefit/lowest risk intervention, because that may carry a cost that is unacceptable.

But, you are going to weigh these attributes and then make a decision, one likely better than if these attributes were not explicitly measured.

In constructing the model, the first and most important issue is: What is the question? In our case, the question is not “Which is the least expensive medication?” but, rather, “What is the complex of care activities, including medications, that leads to the best outcome for the patient suffering from depression, given existing resource constraints?” Even though we have four possible combinations of cost and outcome, you might not choose the item that gives you the best outcome, because you also have to consider cost.

So, the question in treating depression, and other illnesses that relate to depression, is not “Which is the least expensive medication?” but, rather, “Which medication provides the best outcome for the money and also addresses other health needs associated with the diagnosis?”

An exceedingly narrow focus is a downfall of many models. Such models try to tease apart the index condition from everything else, though we know that this cannot be done accurately. It cannot be done clinically because of the interactive effects of multiple diagnoses, and it cannot be done economically because you cannot separate what is truly related to that index condition as opposed to all other diagnoses. It is an economic problem called the “joint-product issue.”

For example, you cannot really separate depression from heart failure or hypertension as clearly as one would like. You can never get a really good estimate of the cost of any diagnosis independent of everything else. That is why (a) in economics, just as in clinical medicine, we try...
to do control studies — preferably, prospective randomized control studies — and (b) we do not ask the question, “What is the cost of treatment for X but instead, we ask, what is the cost of caring for people who have the diagnosis X versus those who do not have the diagnosis?” Given the unknown, interactive, and often geometric consequences of trying to treat correctly, what we want to know in this case is the cost of caring for people with depression.

An analytic model that mirrors the real world can calculate issues of time, patient needs, provider requirements, and those of payers, employers, and insurers. You can deal with all of these inputs simultaneously as you measure the effects of changing reality — for instance, changes in disease prevalence or cost of hospitalization. Remember, every time there is an intervention, the overall reality changes.

One of the strengths of models is that they can be adapted easily to individual institutions and circumstances. You can change input variables, such as cost and treatment patterns, to make the model unique to your organization. These changes can be tested by asking, “What individual and interactive effects will occur with inpatient days, medication costs, long-term benefits, long-term costs?” Models are infinitely flexible if you want to make them that way.

Finally, modeling can estimate the clinical and economic outcomes of all likely alternatives; one of which always is to do nothing. Modeling is an inexpensive, quick, and systematic prediction. Models even can be used in the absence of any real data, if people agree on what the reality might look like. That does not necessarily mean a good model will follow, but it is a beginning model with a first answer. Boundaries can then be set around what, ultimately, you will do based on confidence in the answer derived.

Correctly designed models will include an abundance of hard data for each aspect of the model inputs (epidemiological, clinical, quality-of-life, absenteeism, cost, etc.). The better the information, the more parameters can be included and the more powerful the model will be in producing the best possible answer for decision makers.
There is a link between response and remission, and the link is time. A responder is anybody who gets 50% better and a remitter is anybody who experiences 70% or better improvement on a HAM-D or a HAM-A questionnaire. Somebody who is responsive without reaching remission is stuck between 50 and 70% improved. These patients are partially better.

After one week of treatment, 0.5% of patients with GAD (the most closely related anxiety disorder to depression) met criteria for remission. After two weeks of treatment 3.5% are in remission. After three weeks, the remission rate is 9.4%, meaning that after three weeks of treatment, more than 90% of patients are not in remission (Figure 1). However, as time goes along, the percentage of patients going into remission continues to increase. After eight weeks of treatment, just short of 50% of patients have met criteria for remission of GAD.

If people remain on a study dose, they will continue to move toward the remission category. The simple principle is to get people well. First you have to get them on an adequate dose, such as the flexible doses that are built into the model. Then you have to keep them on that dosage, because that is what is going to transition people into remission.

Going forward in time, the percentage of those in remission increases such that at the end of eight months, 70% or more of patients are 70% or more improved, even though in the last six months of treatment they are being kept on the same dose. Therefore, once you get them on an adequate dose, remission is a function of time.

Another analysis demonstrates that more severely impaired patients take longer to get to remission. Increasing the dose too aggressively in the beginning, however, has a counterproductive effect in increasing early dropouts.

**Duration of Therapy and Costs**

Minimum effective doses should be prescribed at the beginning of treatment. The dose is then gradually increased at weekly intervals until the optimal therapeutic dose is reached. The patient is kept on that dose. The longer the patient stays on that dose, the more likely the patient will reach remission. But adequate dosing also has an effect on costs, which obviously is to drive up the drug-therapy costs. But with respect to total costs, adequate dosing is saving thousands of dollars. You invest $100 and save $2,500.

In the study by Thompson and colleagues, they looked at patterns of antidepressant use and the relationship to cost of care. Thompson segmented patients into five patterns of usage: early discontinuation, switching/augmentation, upward titration, partial compliance, and the three-month use group. The early discontinuation group, which included patients who received no more than a total of 60 days of treatment with an antidepressant.

**FIGURE 1** Long-term GAD treatment

<table>
<thead>
<tr>
<th>Phase I: single blind</th>
<th>Phase II: double blind</th>
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<tbody>
<tr>
<td>Paroxetine 20–50 mg (N=559)</td>
<td>Paroxetine (N=285)</td>
</tr>
<tr>
<td>Placebo (N=274)</td>
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</tbody>
</table>

*Remission = HAM-A ≤ 7; LOCF data set
SOURCE: GlaxoSmithKline data on file, 2001; Sheehan 2001

*p < .01 vs placebo

**FACULTY PRESENTATION**

**The Importance of Adequate Length Of Antidepressant Therapy**

DAVID V. SHEEHAN, MD, MBA

**FIGURE 1 Long-term GAD treatment**

% Remission

<table>
<thead>
<tr>
<th>% Patients</th>
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<th>Phase II: double blind</th>
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</thead>
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<tr>
<td>80</td>
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Randomization

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<td>% Patients</td>
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<td>60</td>
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<td>70</td>
<td>60</td>
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</tr>
</tbody>
</table>

*Remission = HAM-A ≤ 7; LOCF data set
SOURCE: GlaxoSmithKline data on file, 2001; Sheehan 2001
sant over a 12-month interval, had total mean medical costs of $5,610. By contrast, those in the three-month use group who were considered compliant and received at least 90 days of therapy with their initial SSRI (no switching/augmentation or upward titration) had total mean costs of $3,393 over the 12-month follow-up period. This complements Revicki’s finding on overall cost expenditures.

Adverse Events and Early Dropout

Premature dropout is a major cause of relapse and recurrence. In meeting the challenge of early dropout, treatment outcomes are enhanced by improving compliance. In the earlier mentioned McComb’s study of Medicaid patients prescribed antidepressants, only 22% remained on therapy for an adequate treatment term of six months.

The reasons for high dropout rates are largely adverse events: 62% of early dropouts and 67% of late dropouts cited adverse events as the reason why. But lack of effective response also contributes. Lin (1995) looked at dropouts as a function of time, and the data show the same thing consistently: The highest dropout occurs in the first 4 to 8 weeks because of side effects. Therefore, poor tolerability leads to early dropout of SSRI treatment.

The question now becomes, “What are our current drug options that will improve compliance, reduce adverse effects, decrease time to effectiveness, improve patient outcomes, and save costs to the managed care system overall?” Remember, we need to treat people to remission to protect them against relapse in the long run. We will describe a fairly new technology that looks promising in helping us achieve some of these goals.

**Controlled-Release Medication and Outcomes**

Sky Pharma has a new technology that controls the amount, timing, and location of drug release. The tablet has two basic components, a core that contains the active drug plus barrier layers that swell, gel, and erode to control drug diffusion into the gut.

This technology was used in the controlled-release formulation of paroxetine (paroxetine CR). Twelve-week follow-up studies were conducted in 640 depressed patients. After a placebo washout, patients were randomly assigned to either paroxetine controlled release (CR), paroxetine immediate release (IR), or placebo. The doses of paroxetine CR were titrated from 25–62.5 mg and from 20–50 mg for paroxetine IR, which are equivalent given that there is only an 80% release of drug from the paroxetine CR technology. At the end of the study, patients were tapered off the medication.

The results of the study illustrated that both formulations are statistically superior to placebo, as measured by decreases in HAM-D scores. Paxil CR and Paxil were comparable in efficacy. If the CR is giving a slightly better effect, are the side effects greater and does this have an impact on rate of dropout? We would expect that with marginally better efficacy, we would see marginally higher adverse events and dropout rates. What we found was exactly the opposite.

We examined the number of dropouts due to all adverse events among patients on Paxil CR, Paxil IR, and placebo. Even though Paxil CR provides comparable efficacy, a low rate of dropouts due to adverse events was noticed for patients in the Paxil CR arm (Figure 2). This may be due to slightly less nausea with Paxil CR, to which patients generally develop a tolerance after about three weeks. And while we have not completed the studies that will assure us that these data will translate into a meaningful economic effect, at least they are directionally correct.

Another issue is the small weight gain seen over time on all SSRIs. What we found is that more people lose weight (7% of body weight) with Paxil CR than gain weight over 12 weeks of treatment. We are not entirely sure why this is happening, but one of the hypotheses is that CR is being absorbed lower down in the GI tract. It is bypassing the aggregate of 5HT3 receptors in the upper GI tract that is believed to be involved in satiety. Another hypothesis is that since more of the medication is getting

![FIGURE 2 Overall drop-outs due to AEs](https://example.com/image.png)

* p = .0008 Paxil vs. placebo
Data on file, GlaxoSmithKline
to the lower GI tract, you get a slight increase in hyper-motility of the gut, which will increase elimination and may be the reason some patients lose weight on CR.

Paxil CR has equal efficacy with reduced side effects, which may well keep patients compliant longer. That should lead to better compliance, reduced costs, and an increased number of remissions, all the outcomes we are pursuing.

References
DEMONSTRATION OF AN ECONOMIC MODEL

The SSRI Therapeutic Effective Dose Model

MIKE DERKACZ AND TIM REGAN, RPH

The SSRI Therapeutic Effective Dose Model is a collaborative effort by many people, including David Sheehan, MD, MBA, and behavioral health care thought leaders, and health care economists and consultants at Applied Health Outcomes. The approach in building the model has been to try to understand the key objectives of managed care decision makers and clinicians in treating depression, or, expressed differently, to accurately define the research question.

This Effective Dose Model (EDM) looks at package-insert starting doses for selective serotonin reuptake inhibitors (SSRIs) on one end of the spectrum; average doses used in practice, or “real-world doses”; and the FDA flexible dose trials to establish the gold standard for effectiveness. The model allows the user to simulate the relationship between health care utilization/costs and plan-specific usage of SSRIs at varying doses along this continuum.

The Revicki study is an important, albeit conservative, component of the model because it demonstrates a distinct reduction in costs for patients utilizing drugs at an adequate dose versus inadequate doses. Overall, the studies that fuel the model must be credible, well-referenced, and transparent. Additionally, the model is flexible and enables users to enter their own data and is thus customizable. It is easy to use and intended to be practical and valuable for managed care decision makers and clinicians — the target audience.

The model is divided into five sections: an overview of depression and best current knowledge regarding optimal therapy, a current utilization screen calculator, a dose adjustment screen, a market share simulator, and a length-of-therapy calculator.

The overview section addresses the economic burden of depression and anxiety, prevalence, FDA-approved indications for several SSRI antidepressants, total costs of adequate versus inadequate treatment, the FDA flexible-dose trials, the challenge of early therapy dropout, rates of remission, and a 90-second vignette of Sheehan discussing the economic and clinical consequences of inadequate dosing.

Current SSRI Utilization

The fundamental question in the model is: What is the economic impact of using inadequate dosing in a real world environment? Figure 1 is the first input screen of the model, where the number of lives in a plan can be entered.

Assume that a plan has 1,000,000 lives. SSRI utilization data from Scott-Levin Physician Drug and Diagnostic Audit (PDDA) serve as the default, yielding 3% or 30,000 members on an SSRI. Alternately, a plan’s own utilization data may be used.

The critical driver of the model — total medical costs associated with an adequately treated versus an inadequately treated patient — is based on Revicki and Thompson’s work. Total medical costs are based on two studies, as referenced by the blue books. The Revicki differential is conservative at $1,500 annually, while Thompson may be more accurate at $2,217 annually. Revicki found that, treated with an adequate dose of antidepressant therapy, a member would cost the health plan $3,744 (in 1994 dollars) over a 12-month period. This includes all inpatient, outpatient, laboratory, and medication costs. The same 12-month cost for an inadequately treated member was $5,244, yielding an incremental difference of $1,500 per year.

Should the Revicki numbers be considered too conservative, the Thompson data may be used as an alternate default. Thompson’s cost differential between an adequately and an inadequately treated patient is slightly higher, at $2,217. A plan’s own data can be entered here as well.

The definition of adequate treatment, which is found in the Revicki reference, is three months at 10 mg of fluoxetine, 75 mg of imipramine, or 75 mg of desipramine. The user may insert any cost values — either from other published studies or from his or her own plan’s data — as adequate versus inadequate, so the incremental difference is entirely user-dependent unless the default is used.

In Figure 2, selecting Paxil brings up these columns: Current Units, which is actually the number of pills dispensed by dose; Patient Distribution, which gives per-
percentages of patients on these varying doses; the Default Distribution (from national benchmark data); the Number of Patients those percentages actually represent in our sample million-member plan; a DACON (daily average consumption) by dose; the Default DACON; and at the very far right, the “average milligrams per day.” Most plans have pharmacy-level data that can be entered. Values load automatically for each of the four products. A desirable DACON is a 1.0 for each of those particular doses.

**Dose Adjustment Screen**

Working with data elements on the Dose Adjustment Screen allows a user to look at both a flexible dose trial cost impact and a “real world” economic impact. The real-world selection brings up the plan’s utilization data or the national Scott-Levin default data for mean dosages, represented on the scale by the blue hash mark. For Paxil the national default is 24 mg, fluoxetine 25 mg, Celexa 27 mg, and Zoloft 81 mg. Costs for each product are derived from WAC (wholesale acquisition costs) comparison at the therapeutic effective dose. Users can, however, change any of these costs to reflect reality at their organization.

From here, users of the model can view the cost detail of real-world doses. If one were to click on the View Cost Detail Box (data not shown), the total cost of adequately treated and inadequately treated members, the pharmacy costs, per patient costs, and total costs for all four products would be shown. These numbers were derived by using the Revicki figure of $3,744 for adequately treated patients times the number of patients and $5,244 times the number of inadequately treated members.

This screen shows that the closer the agent’s therapeutic dose is to the real-world dose, the more adequately controlled the population will be; resultant economic benefits are also displayed (Figure 3).

From the model, it appears that fluoxetine should be selected because its numbers are best, and fluoxetine is already on the first tier of every formulary because it is generic. Fluoxetine is ideal for pure depression, but Paxil may be better for anxiety plus depression, based on the breadth of indications and proven effectiveness in all major anxiety disorders. The price of generic fluoxetine will always be lower, but the question is now, “How do I manage my patients optimally and what are the best options I can provide them?” The model attempts to answer those questions for the SSRI class.

**Rationale for the Therapeutic Dose**

If one selects the Flexible Dose Trial “Baseline” hyperlink, each of the individual bars is raised to the level
of the “flexible trial dose” or therapeutic effective dose, which is the dose required to reduce HAM-D scores by 50%, thus demonstrating efficacy. Based on the studies submitted to the FDA to achieve this reduction in HAM-D, the flexible dose required for Paxil was 27 mg; fluoxetine 25 mg; Celexa 62 mg; and Zoloft 159 mg. These doses may seem high, but they are the best evidence-based data we have.

The model, however, also includes 20% lower “Alternate” doses within the Flexible Trial hyperlink. Users of the model can select these more conservative doses if they feel more comfortable doing so. In the final analysis, though, the only data that a user should rely on are the data that have been audited by the FDA and received its approval. These are the pivotal, regulatory studies that were the basis for the approval of different indications and that were built into the model. They are the best evidence that anyone currently has.

If all patients were prescribed and consuming a therapeutic dose, they would be adequately treated and the per-patient, as well as total, costs would be fairly close across all products.

**Market Share Simulator**

The objective of this component of the model is to allow the user to manipulate current market shares for the SSRIs to examine the relative impact of total adequately treated members and the relationship to economic impact.

Figure 4 demonstrates the Budget Impact of an equal market share of each SSRI, as well as an adjusted market share, at real-world doses. However, the model user might say, “If Paxil and fluoxetine provide a better opportunity to achieve an adequate dose because their real-world doses are closer to therapeutic doses, then if I increase the Paxil and fluoxetine market shares to 35% and reduce Celexa and Zoloft to 15%, I will be able to see how that affects cost and percentage of members adequately treated.” When these market shares are changed, costs decrease by $21,017,433 and the percentage of adequately treated members increases to 85% (from 79%, data not shown). Of course, users can enter their own market share data if they have them to see how it affects percentage of members adequately treated and how it affects overall costs.

**Length of Therapy**

The last model screen enables users to see how length of therapy affects costs. Based on the Thompson paper we discussed earlier, we saw $3,393 in total costs for patients treated for 90 days or more versus $5,610 for patients treated for less than 60 days (Figure 5). The Early
FIGURE 3  Dose adjustment

Dose Adjustment

Cost of Treatment

Paxil®  Fluoxetine  Celexa™  Zoloft®

Per Patient Total

% Adequately Treated

Pharmacy Cost  Baseline  Alternate  Flexible Dose Trial  Real World  Starting Dose

Adjust Dose

FIGURE 4  Market share simulator

Market Share Simulator

Current  Adjusted

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percent of Members</th>
<th>Number of Members</th>
<th>Total Cost</th>
<th>Percent of Members</th>
<th>Number of Members</th>
<th>Total Cost</th>
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</thead>
<tbody>
<tr>
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<td>36.00%</td>
<td>3,666</td>
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<tr>
<td>Celexa™</td>
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Impact*  ($2,101,743)

Budget Impact

Adequately Treated

* A negative impact implies a projected cost savings to the plan.
Discontinuation (≤60 days) and the Three Month Use (≥90 days) buttons enables users of the model to see how different patterns of SSRI usage affect their plan’s health care utilization and specific cost areas. The HEDIS button in the upper right hand corner of the slide can be clicked on to show audited, state-by-state performance data on SSRI length of therapy (a HEDIS performance measure).
Assessing the Utility of and Implementing The SSRI Model Within Managed Care

F
ollowing the faculty presentations by David Sheehan, MD, MBA, Bernard Bloom, PhD, Tim Regan, RPh, and Mike Derkacz, a group of physicians, psychiatrists, and pharmacists discussed what they had heard with a particular emphasis on how the information validated the Effective Dose Model or left them with additional questions. The meeting sponsor and the moderator, Neil Solomon, MD, Senior Associate of The Zitter Group and President of NAS Consulting Services, were especially interested in capturing ideas about how the model could be enhanced and become a more useful tool for other managed care thought leaders and decision makers. The following pages include excerpts from this discussion.

One of the Economic Working Group participants, Paul Monson, MD, brought data to the meeting to be shared with the group and used as a real-world case study. After entering the data into the Effective Dose Model, Dr. Solomon asked for responses to the utility of the model and the target audience that might find it useful.

NEIL SOLOMON, MD: The numbers in the model are driven by a combination of adequately treated plus inadequately treated patients. When the inadequately treated share is large, the overall cost will be large because the delta in per-patient costs is large based on the data from Revicki. What we found when we loaded in Paul Monson’s pharmacy data was that Paxil and fluoxetine have low costs for inadequately treated patients. How does that resonate with you, Paul?

PAUL MONSON, MD: That sounds intuitively correct and would have a potential application. For example, I could take the model calculations based on our own pharmacy data and talk to each physician regarding their prescribing patterns and the associated costs. I could tell them if their top drug is Zoloft and discuss the adequacy or inadequacy of their dosage. The other way I could use the model is to demonstrate the cost of inadequate treatment, the potential cost of inadequate dosing.

ELSON KIM, PharmD: Can we assume from this model that if we adequately treat the depression, then all of the
costs related to the comorbidities of those depressed patients will go down due to decreased admissions?

SOLOMON: I’m seeing nods from Tim and Mike.

TIM REGAN, RPh: Yes. The Revicki data suggest that adequate treatment of depression will have the most positive impact on reduction in nonmental health-related inpatient costs.

KIM: Then we should be able to use this model on past data, i.e., two-years post against one-year post data and be able to demonstrate a savings. So, for instance, if your market share for fluoxetine and Paxil was lower in 1998 than it was in 1999, you should be able to demonstrate savings in this model as well as in reality. I think that validation of past data sets and savings demonstrated from them would be a very powerful message that would validate the tool going forward.

SOLOMON: Right. I think there are actually two things that I teased out of what you are saying. One regards the Revicki data on cost differentials between adequately and inadequately treated patients and how to generate that delta in your own environment to determine whether or not these savings are true in your plan. The other thing I heard you say that could potentially be valuable is to see if this model really works prospectively. For example, if you move people onto the medications that you think are at more adequate doses, then let’s watch and see what happens to our health care costs in that population.

KIM: Correct. Because if you could pull cost data back from 1997, prior to Celexa coming on board, then you would only have had three choices, Paxil, fluoxetine, and Zoloft, and you could see a direct impact of Celexa as market share grew relative to your associated cost going up.

SCOTT SPROULL: I think that’s key because you’re validating Revicki to determine if costs associated with inadequate and adequate treatment are similar to what you see in your own data.

KIM: Revicki is the pivotal trial that this work is based on. So if you validate those data as being accurate, this tool also becomes accurate.

BERNARD BLOOM, PhD: It isn’t only cost that we are trying to control or to measure. We are also looking for some of the indirect effects that have profound cost ramifications but are outside the medical care system, such as quality of life, normal activities, and daily function. Remember, the goal of health care is not to save money. It is to improve health first and to improve it within your given budget. So, when you treat people correctly, the largest effect in terms of economics is probably going to be felt in the area of work loss and reduced productivity. Inadequate treatment costs would probably end up being 10 times greater if you calculated what the indirect effects would be. Unfortunately, it is only recently that employers have begun to pay attention to that because historically they have been focused on the cost of their premium and nothing else. Again, the cost of the premium is very small compared with all the other employee-related costs like work loss.

MONSON: We are doing health care assessments for employers and the top two are migraines and depression in work — both relating to productivity reduction.

DIANE AMMERMAN, PharmD: I do employer group analysis on a monthly basis, and the employers are just like sponges. They want this type of information. They want to justify paying for antidepressants, paying for MS drugs. So for me, the calculations in this model would be of value.

SOLOMON: If an interactive model that captures indirect cost were built based on this theory of adequate dosing, you would likely see a difference in the cost of the agents. Employers typically do not like to recommend specific products be used. Does anyone want to comment on that?

LARRY WOLK, MD, MPH: I don’t think there is any utility at all in taking such a model to the employers because if they are working through a health plan as their third party administrator, they do not have control over the formulary. You may actually work against the managed care company that is involved in this because it may go counter to whatever national formulary they might be using.

MIKE DERKACZ: How about a PBM dealing with a large, self-funded employer, like GE? Would that have utility?

WOLK: Yes.

SABAH CHAMMAS, MD: In our environment in California, we cannot contract directly with employers except in the area of EAP. So I envision a situation where I would go to an employer and say we have tools to help you with absenteeism — which in EAP is crucial — and if you allow us to manage this we can save you money. Then they would not have to be directly involved in formulary. So I see some use in a model like this just to show the employer that we have tools to help them reduce work loss.

SOLOMON: So EAPs and self-funded employers would be alternative marketplaces where the model might have direct value. Additionally, since the message of the model to the employer is that adequate treatment is critical, then you leave it to the employer to have a conversation with the plan to say we want to make sure that our people are adequately treated.

The group then had a discussion about the validity of using a population-based approach to determine the percentage of members adequately treated. Dr. Wolk suggested simply running a query on all members that are on less than 26 milligrams of Paxil. Dr. Bloom presented an alternative approach.
BLOOM: The other way to attack it is through the HAM-D. If, for example, your organization does the HAM-D with some regularity, you can look at the issue on distribution of response. Some people will get that 50% improvement on the HAM with 25 milligrams and others will need 100. So that the query you need to ask is not what is the dose, but what is the response? And if it is 50% of the population irrespective of dose that is getting it, then that is denoted as adequate treatment.

DAVID SHEEHAN, MD, MBA: Exactly.

SOLOMON: In answer to your question, Larry, if you could take the HAM-D and train your physicians or clinicians to use it, they could titrate doses to a 50% or better improvement level. That would be a per-patient way of trying to effect what the model is simulating: the dose at which people are most likely to achieve adequate treatment.

DERKACZ: I would like to ask questions on that. We have discussed changing physician behavior. I want to find out, realistically speaking, are you ever going to be able to get physicians to titrate to adequate doses, or are you more likely to be able to control or influence the products they prescribe? In other words, how in the world would you get a physician who is using Celaexa 20 mg to use a higher dose of Celaexa? To me it would be a much easier task to actually do formulary management rather than discourage use of Celaexa and so on.

JEFF WEILBURG, MD: One of the original key drivers in the acceptance of managed care was to reduce variances in practice patterns. So we must look at inappropriate variance and try and how to evidence-based best practices to reduce that variance. You can guide primary care doctors through use of a formulary. The problem is that most of them do not do a HAM-A or a HAM-D, so they have no outcome as we have for blood pressure or cholesterol. If you can get them to do a simple psychiatric rating scale, that is great because as was just pointed out, what you are really teaching them is to clinically manage to remission. Absent that, you can give them administrative data, which is a proxy that gets them part of the way there.

YI ZHENG, PharmD: In terms of looking at the flexible-dose trials, are we making the assumption that the characteristics of the patient population in different clinical trials are comparable across different products? That is a big assumption in itself.

SHEEHAN: Yes, based on the best evidence that there is.

SPROULL: Generally, most depression trials have a pretty much consistent entrance HAM-D of around 23 to 25. So the patient populations are not radically different in most flex dose studies. We just have to make sure that our model calculations are based on FDA-submitted trials. If they are, then they have basically the same exclusion-inclusion criteria.

WEILBURG: Revicki does something similar, but in all of the literature on adequacy, nobody gets 84%. The max they get is 50 to 55%. The validity of that 84% is based more on how many people got average doses.

SHEEHAN: We are trying to take a rather liberal definition of what an adequate dose is. This is absolutely not treating people to remission. So, in fact, the doses required to treat people to remission are higher. This is almost like a worst case scenario but still being able to separate out from placebo. Beyond that, there are further increments of improvement that would be dictated by increasing the dosage.

SOLOMON: A point was made earlier that we need to constantly be reminded what we are talking about by adequate dose. Maybe adequate treatment or adequate dose is the wrong term to use. David, what would you call this? If it is not adequate and it is not reaching remission, what would be a better definition?

SHEEHAN: Minimal treatment, minimal dose required.

REGAN: What you are saying, then, is that your minimum treatment threshold dose for Zoloft is 159 milligrams, but are people going to buy that?

SHEEHAN: That dosage brings about the desired outcome, which is in this case defined as a 50% reduction of HAM-D. That is the criterion. We are not even talking about remission. So, if you cannot get to this level, you are not even in the game any more. That is the point of the model. We are not shooting for the stars, we are just trying to get the world onto the playing field. It is an incremental advance.

REGAN: Just a key distinction. Remember that the economic impact of adequate versus inadequate from Revicki was derived from 10 milligrams of fluoxetine, which was considered effective. So, the point is we are seeing a cost benefit even with subtherapeutic doses. That is why I think the conservative assumptions in the model are all reasonable because the cost differential is even demonstrated at subtherapeutic doses. So if we are getting docs to use higher doses incrementally, that could have an even more positive impact on health care utilization costs.

SOLOMON: Underlying questions are, “Do I believe the
model, does it reflect reality, and is it useful?” Or is the model so conservative that it estimates the absolute lowest amount that I would expect to save? So, have the designers of the model stacked the deck against themselves and, therefore, should I have a lot of confidence in it? It took me a little while to sort that out for myself, but I think what I am hearing is that minimal improvement in the HAM-D, the 50% reduction, would be considered a clinically inadequate improvement by psychiatrists’ standards. Even with that, when we plug it into the model, we get significant dispersion. My recollection from the Revicki article is that they did not even have a difference in the HAM-D between the two treatment groups.

SHEEHAN: That is right. Those scores all started around 14, in both groups, and ended up at 8 to 9, also in both groups. And yet, in spite of the same end points, the economic outcome measures were dramatically better among adequately treated patients. The lesson I took from that paper was that these economic measures are more sensitive outcome measures for depression trials than are the HAM-D.

CHAMMAS: Let us say that I went to a medical group. Most of them don’t take risk for commercial pharmacy anymore, but they take risk for the medical costs. They are going to argue with me that 60 milligrams of Celexa is too high and that 159 of Zoloft is too high. David, can you come and give a talk to our doctors and explain which doses are considered adequate, because I am imagining that I am going to be questioned most diligently on this?

SHEEHAN: My understanding is that the FDA has recently made a decision that when it gets a new submission, it will include in the package insert the flexible doses that were needed for that indication. So we are going to see an accumulation over the next several years of this very information that we are using in this model in the package inserts (and reflected in the PDR). If clinicians do not believe it, you can actually open up a PDR and say, here it is right here, here are the doses.

SOLOMON: We have been talking a lot about the definition of successful treatment. Is 50% reduction in the HAM-D enough, or is there another way to represent this? What do we mean by remission, a key determinant of which is duration of therapy?

SHEEHAN: So what is the ideal duration of therapy?

SOLOMON: For all patients?
and so forth. The length-of-therapy information was very useful and can be presented to the HMO, to PCPs who are capitated, to managed care organizations, and to the employers, because they’re always wondering about those costs.

WOLK: The most important point for me was the Revicki study data. What it makes me want to do is go back and take our health plan data and see if I can validate the Revicki findings because that is what the whole model is based on. If I do, then the model will have a great deal of utility and value for us and give us a lot of power in presenting it to other plans.

AMMERMAN: The biggest take-away for me was the medical offset data. We have been searching for that and it is hard to find. So I am anxious to get some of the copies of those papers and be able to take them back because this is really a hot topic all the way up to our CEO. She wants to know every month why we are spending so much money on SSRIs. So this could justify to her what we are doing. In terms of using the model, it would be useful with certain physician groups with which we are getting into academic detailing. This activity is aimed at improving HEDIS scores and/or increasing length of therapy for depression.

WEILBURG: My take-aways relate to the diagnosis and recognition of anxiety and depression among primary care doctors versus specialists. I would love to share that with my primary care groups. One other audience for the model might be the chairman of the board of the health plan. The people in pharmacy have to worry about what is happening next quarter. The medical director has to worry about utilization. The CEO has to worry about this year and where the money is going to come from. But the chairman of the board wants to have his or her health system provide the best quality, and chairmen generally take a longer view. They are the people who are going to be responsive to this kind of material. And finally, I want to go back and validate the findings of Revicki.

MONSON: Intuitively I knew that depression increased overall medical costs, but now I have got some validity for that, which I can also take back to my plan. First, I am going to use the model for physicians. Second, I would like to use it to demonstrate to our CFO how all of these issues in treating depression affect overall medical costs. I am also going to go back and run our data to see what I can come up with.

ZHENG: One thing that I found interesting was the approach of using information from flex dose trials to look at adequate dosing issues. That is certainly very different from the traditional definition of dosing regimen usually outlined in various guidelines. The other thing that I found very interesting was the OCI data. I understand the data are proprietary, but any detail GSK could share would certainly offer more support to the medical offset theory. In terms of the model, I think this is a good starting point. I am pretty familiar with the literature presented here. One of the things I have been working on is to tap into our integrated medical pharmacy database to validate the type of information that is contained in Revicki and in this model. It will be critical for users of this model to validate the theory themselves through internal data analysis, which could be resource intensive. The bigger challenge is that once you prove that antidepressant treatment compliance could result in improved clinical outcomes and cost savings, how do you affect the current practice and utilization pattern? Over the past 10 years, all the health plans and managed care organizations have been trying to push evidence-based medicine based on either AHCPR or APA guidelines through various programs. Even with all those efforts, we still fail to achieve adequate treatment with this drug class if you look at HEDIS scores. So the bigger issue is: How do you actually have the providers adopt evidence-based standards of practice?

JOHN HERYER, MD: I was aware of the depression statistics regarding compliance and costs, but Dr. Sheehan’s presentation again crystallized that and drove it home. Also, it is important and very hard to collect those data and present them in such a cogent way.

SHEEHAN: I learned a great deal. It was just fascinating. I felt that we were having a look into the future. But one of the things I took away relates to my interest in outcome measures. It may well be that many of these economic cost measures are more sensitive outcome measures in the long and short run for depression than the traditional ones that we are using. I see a time in the future when economic cost measures may become primary outcome measures in depression studies, and then the economic needs of society will match up with the needs to deliver superior treatment results.

For additional information about building a health economics model using your own data, contact Tim Regan, RPh, Applied Health Outcomes, at the following e-mail address: tregan@applied-outcomes.com