

SUPPLEMENT TO

M A N A G E D

Care

Undertreatment of Depression And Comorbid Anxiety Translates Into Costly Mismanagement of Resources And Poor Patient Outcomes

Proceedings of the Economic Working Group Advisory Board
March 4–5, 2005, Miami

HIGHLIGHTS

- Why and to what extent depression and comorbid anxiety are underdiagnosed and undertreated in our society
- How the Health Plan Employer Data and Information Set (HEDIS) tracks and documents substandard treatment of patients with depression
- What major stakeholders in health care can do to improve care and outcomes for patients with depression and comorbid anxiety
- The clinical and economic importance of compliance with medication therapy
- National trends in the pharmaceutical treatment of anxiety

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Care

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INTRODUCTORY MESSAGE

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All major stakeholders play a role in improving the care of patients with depression and comorbid anxiety. These stakeholders include physicians, managed care plans, employers, federal and state governments, pharmaceutical manufacturers, and patients. Primary care physicians treat the majority of patients with depression; according to the published literature and national standards for the quality of care, however, they do a substandard job. Patients treated by psychiatrists have only marginally superior outcomes.

Managed care organizations that frequently adopt generic step therapy programs in an effort to reduce their pharmacy budgets might do well to reexamine those programs in light of the overall medical cost to the system and the quality of care that their patients receive. Employers could improve care for their employees and retirees with depression by universally supporting proven disease management programs. The federal government, through the new Medicare Prescription Drug, Improvement and Modernization Act, presents an opportunity to provide seniors with Medicare drug coverage, including expanded coverage for antidepressants with superior safety and efficacy profiles.

The pharmaceutical industry can contribute to improved patient outcomes by providing the marketplace with the safest and most efficacious products to treat depression and comorbid anxiety. A medication regimen that is highly tolerable is one with which patients will comply more readily. Patients also follow instructions and absorb messages more effectively when primary care physicians and psychiatrists give patients instructions and educational messages. This improves patients' compliance with antidepressant medication regimens, as well as their clinical outcomes and quality of life.

All these components play a role in improving the quality and cost-effectiveness of care for patients with mental health diagnoses. Nevertheless, according to nationally recognized indicators of quality, such as the Health Plan Employer Data and Information Set (HEDIS) Antidepressant Medication Management Measure, treatment of patients with mental health conditions is substandard and resists any significant improvement.

This publication explores the various ways in which major stakeholders might contribute to an overall improvement in the quality of care. It will review the economic impact of substandard care and of noncompliance with current pharmaceutical treatments for depression and anxiety. Lastly, it will provide data on the key benefits of controlled-release paroxetine (Paxil CR), which is a controlled-release selective serotonin reuptake inhibitor that is approved for the treatment of depression, panic disorder, social anxiety disorder, and premenstrual dysphoric disorder.

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ABOUT THIS PUBLICATION

The ongoing documentation in the medical literature of the underdiagnosis and undertreatment of mental illness in the United States is a motivating factor for the sustained efforts of the Economic Working Group (EWG) Advisory Board. The EWG, composed of professionals from managed care, behavioral health, psychiatry, pharmacy, academia, health care policy and accreditation, primary care, health economics and outcomes research, and the employer sector, has been convening regularly since 2002.

The most recent advisory meeting took place on March 4 and 5, 2005, in Miami. Many of the primary discussion points of that meeting are reflected in the following pages. This publication is not a simple synthesis of the meeting, however. It also draws on literature in the MEDLINE database, with faculty insight inserted where appropriate and illuminating. Fac-

ulty input provides readers with a real-world context for the literature presented.

Optimal or even adequate treatment of depression and comorbid anxiety will require the efforts of a multidisciplinary team within the health care setting, and will require the alignment of stakeholders' interests. Without such alignment, substandard and fragmented care will continue to be the norm. For example, if capping the pharmacy budget (with little or no consideration of the effect on overall medical costs, workplace productivity, the quality of life, or clinical outcomes) remains the dominant paradigm in some managed care systems, little progress will be made in the diagnosis and treatment of patients with mental illness. The aim of this publication is to clearly explain how each of the major stakeholders can transform this unfortunate situation.

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DISCLOSURE OF SIGNIFICANT RELATIONSHIPS

Michael T. Eaddy, PharmD, PhD, has received grant and research support and consulting fees from GlaxoSmithKline.

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David V. Sheehan, MD, MBA, has received grant and research support and consulting fees from GlaxoSmithKline. He also is on the GlaxoSmithKline speaker's bureau.

Undertreatment of Depression and Comorbid Anxiety Translates Into Costly Mismanagement of Resources and Poor Patient Outcomes

THE EPIDEMIOLOGY OF DEPRESSION AND COMORBID ANXIETY

As with most chronic diseases, the treatment of mental illness involves a host of stakeholders, all of whom play a role in improving the quality of care that patients receive. In addition to their shared challenges, stakeholders face individual challenges that are unique to their environment. The following section is an overview of challenges that commonly arise in the treatment of depression and comorbid anxiety, followed by a discussion of the individual challenges that confront each of the major stakeholders.

One core problem facing all those involved in the treatment of mental health disorders is the prevalence of the illness in our society. The literature documents the lifetime prevalence of major depressive disorder (MDD) at 16.2 percent of the population, or 32.6 to 35.1 million U.S. adults. Twelve-month prevalence rates translate into 6.6 percent of the population, or 13.1 to 14.2 million U.S. adults experiencing an episode of MDD in a given 1-year period (Kessler 2003).

A growing body of literature also demonstrates significant undertreatment of MDD. Approximately half (51.6 percent) those who suffer from MDD receive treatment for it. This figure alone should raise alarm, but more disconcerting is that of those who do receive treatment, only about 42 percent are considered adequately treated. Thus, fewer than 22 percent of all persons suffering from MDD are treated adequately. Kessler and colleagues (2003) conclude: "While the recent increase in treatment is encouraging, inadequate treatment is a serious concern. Emphasis on screening and expansion of treatment needs to be accompanied by a parallel emphasis on treatment quality improvement."

Literally dozens of epidemiological studies document the epidemic of undertreated depression. Substandard treatment is frequently characterized by a lack of follow-up along with high rates of inadequate antidepressant treatment by primary and specialty care providers.¹

Regarding anxiety, the literature states that 1 in 4 Americans will experience an anxiety disorder at some point in their lives. This translates into a lifetime prevalence of 24.9 percent and a 1-year prevalence of 17.2 percent.

Surprisingly, the prevalence of anxiety disorders is greater than the prevalence of major depression, yet there

is only a minor emphasis on anxiety in managed care organizations. There are also no national evidence-based guidelines for the treatment of anxiety; the American Psychiatric Association (APA) guidelines address only post-traumatic stress disorder (PTSD) and acute stress disorder (Arikian 2001).

Anxiety is a constellation of disorders, many of which are understood poorly. The most commonly recognized anxiety disorders include acute stress disorder, PTSD, panic disorder, obsessive-compulsive disorder (OCD), social anxiety disorder (SAD), and generalized anxiety disorder (GAD). Anxiety is highly prevalent, comes in many forms, and can be chronic — with frequent episodes lasting longer than 6 months. Little is known about the factors influencing the duration of GAD, and relapse is a common occurrence. Using Kaplan-Meier curves to assess the likelihood of GAD remission in 167 patients, testing at 6- to 12-month intervals for 5 years, researchers found the rate of GAD remission to be only 0.38 (Yonkers 2000).

MENTAL DISORDERS AND SYSTEMS ISSUES

Despite their high prevalence, high likelihood of recurrence, and the reliability of available diagnostic tools, mental disorders either are missed or intentionally not coded as a primary or secondary diagnosis. This is supported by studies showing that more than 30 percent of patients initiating antidepressant therapy did not have a coded diagnosis for either depression or anxiety (Eaddy 2003b, Sheehan 2004). Several explanations exist:

- Depression is a common comorbidity of many chronic diseases, and this comorbidity complicates accurate diagnosis.²
- Within many managed care benefit designs, the nonparity of medical and behavioral health benefits serves as a barrier to adequate diagnosis and treatment of patients with depression and anxiety.³

¹ Charbonneau 2003; Dawson 1999; Keller 2001, 2002; Ohayon 2002; Parikh 1999; Salzman 2001; Simon 2001, 2002; Steffens 2000; Unutzer 2000.

² Ballenger 2000, Kroenke 2003, Lecrubier 2001, Wittchen 2001, Wittchen 2002.

³ Merrick 2001, Peele 1999, Sturm 1997, Umland 1997

- Due to gaps in managed care payment systems, especially for the primary care physician (PCP), there is a lack of reimbursement for certain treatments (e.g., telephone consults), which discourages providers from extending this kind of service and diminishes the likelihood of optimal care.
- Social stigma against patients with mental health problems still exists and may deter physicians from documenting such disorders.
- Providers may feel that they are ill-equipped to deal with the social, familial, economic, and/or spiritual factors that may play a role in the onset and treatment of disease. Some do not consider these mental health disorders real diseases, but a response to unfortunate social or desperate domestic circumstances (McNair 2002).
- In our health care system today, there is a dearth of well-established reliable systems and clinical practice guidelines that would ensure adequate treatment of patients diagnosed with depression and/or anxiety.

It must be recognized that these issues are entrenched in our health care system and will not be easily changed or mitigated by any organization.

The economics of common mental health disorders

In 2000, the economic burden of depression in the United States was calculated at \$83.1 billion, which included direct medical costs, suicide-related mortality, and workplace costs (Greenberg 2003). Current figures for the economic burden of anxiety are unavailable. Nevertheless, in 1990, annual costs for anxiety were estimated at \$42.3 billion nationwide, or \$1,542 per afflicted person. Greater than half this amount (54 percent) was due to nonpsychiatric medical treatment costs, 31 percent to psychiatric treatment, 10 percent to workplace absenteeism and lost productivity, 3 percent to excess mortality, and 2 percent was spent on prescription pharmaceuticals (Greenberg 1999).

Resources spent on anxiety disorders constitute nearly one third of all mental health care expenditures. Six-month medical costs for patients with anxiety or depression are \$2,390 compared to \$1,397 for patients without these disorders (Arikian 2001). Emergency room (ER) use is a prime example of mental-health-related resource consumption. For example, as many as 28 percent of ER visits are

the result of panic attacks, and 5 percent can be attributed to other psychiatric illnesses (Klerman 1991). The two anxiety disorders associated with the highest use of health care resources are PTSD and panic disorder. All anxiety disorders (other than simple phobia) are associated with impairment of workplace performance (Greenberg 1999).

In summary, depression and anxiety disorders are underdiagnosed and inadequately treated in our health care system, leading to costly resource mismanagement. All stakeholders play a role and have a responsibility to improve the situation. The following section is a quantitative measurement of the inadequacy of treatment.

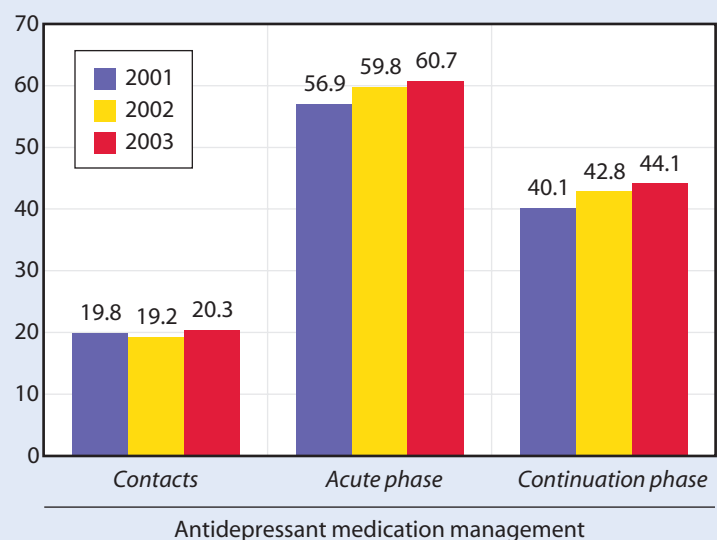
HEDIS: EVIDENCE OF SUBSTANDARD CARE FOR PATIENTS WITH DEPRESSION

Developed by the National Committee for Quality Assurance, the HEDIS Antidepressant Medication Management Measure focuses on compliance with medication regimens and appropriate follow-up as the keys to improved care for patients with depression. The three components of the measure are as follows:

1. Optimal Practitioner Contacts for Medication Management

This is the percentage of members ages 18 and above, as of the 120th day of the measured year, who were diagnosed with a new episode of depression, were treated with antidepressant medication, and who had at least 3 follow-up contacts with a primary care or mental health practitioner during the 84-day (12-week) acute treat-

FIGURE 1 HEDIS effectiveness of care measures, selected commercial averages: 2001–2003



SOURCE: NCQA 2004

ment phase. At least 1 of the 3 follow-up contacts had to be with a prescribing practitioner (e.g., licensed physician, physician assistant, or other practitioner with prescribing privileges).

2. Effective Acute-Phase Treatment

This is the percentage of members ages 18 and above, as of the 120th day of the measured year, who were diagnosed with a new episode of depression, were treated with antidepressant medication, and remained on an antidepressant drug throughout the 84-day (12-week) acute treatment phase.

3. Effective Continuation-Phase Treatment

This is the percentage of members, ages 18 and above as of the 120th day of the measured year, who were diagnosed with a new episode of depression, treated with antidepressant medication, and who remained on an antidepressant drug for at least 180 days (6 months).

Over a 3-year span, the performance of participating HMOs on all these measures has been mediocre, at best, and does not show signs of significant improvement. HMOs reporting HEDIS data cover approximately 90 percent of individuals enrolled in commercial managed care plans; therefore, performance can be considered broadly representative of patient care nationwide. Figure 1 depicts recent commercial plan averages on HEDIS effectiveness of care measures.

The APA has published guidelines that recommend that patients diagnosed with depression continue antidepressant therapy for several months *following remission of symptoms*. (Some patients will require treatment well after the 6-month mark.) Beyond the continuation phase, they guide practitioners in treating depressed patients through the maintenance phase. The below box contains the substance of the APA's published guideline for MDD (2000).

The ultimate goal of the treatment of depression and anxiety disorders is remission, or achieving a virtually asymptomatic state (Ninan 2001). To that end, the Agency for Healthcare Research and Quality (AHRQ) has published guidelines regarding the importance of the

length of therapy for patients with depression. The following is an excerpt from the guideline that covers the medication continuation and maintenance phases (bold-face added for clarity and emphasis):

There is very strong evidence that specific medications prevent relapse/recurrence in most patients with recurrent forms of MDD. Since the episode onset date may not be readily determined, particularly in first-episode patients, **most patients should receive the full therapeutic dosage of antidepressant drug for 4 to 9 months** (the average duration of a major depressive episode) of continuation therapy **after symptom remission is achieved**. In those for whom the onset date is known, a somewhat shorter continuation phase may be attempted, but it should not be less than 4 months. For those with episodes of 2 years or more, it may be wise to pursue a continuation period of at least 9 months. Patients who have a recurrence shortly following continuation therapy withdrawal may require long-term maintenance medication (AHCP 1993).

In 2003, the *Lancet* published results of a meta-analysis that was designed to evaluate the odds of relapse of MDD as a function of length of therapy. Researchers found that patients who remained compliant with an antidepressant course of therapy reduced the odds of relapse by 70 percent, compared with patients who discontinued treatment (Geddes 2003). Other research has found that only a small percentage of patients, generally less than a third, will achieve remission after 6 or 8 weeks of medication therapy. As many as 20 percent of patients will continue to be depressed for months or years after diagnosis and after the initial phase of treatment has ended (Thase 2001).

In spite of these and other studies in the literature and published guidelines, low rates of adherence with antidepressant medication regimens persist. The consequences of this poor compliance are a negative impact on

American Psychiatric Association guideline on the continuation and maintenance phases of therapy for major depressive disorder

Continuation phase

During the 16 to 20 weeks following remission, patients who have been treated with antidepressant medications in the acute phase should be maintained on these agents to prevent relapse. In general, the same dose used in the acute phase should be used in the continuation phase. Although there has been less study of the use of psychotherapy to prevent relapse in the continuation phase, there is growing evidence to support the effectiveness of specific psychotherapy during this period.

Maintenance phase

Following the continuation phase, maintenance phase treatment should be considered to prevent recurrences of MDD. In general, treatment that was effective in the acute and continuation phases should be continued in the maintenance phase. For the most part, the same full doses of antidepressant medication should be continued; use of lower doses of antidepressant medication in the maintenance phase has not been well studied.

How is adherence measured? Defining the Medication Possession Ratio

Adherence to antidepressant therapy can be measured in various ways — measuring the time to gaps in therapy (Gdovin 2004) or measuring the amount of therapy obtained over a defined time period (NCQA 2005). These measures are thought to approximate true compliance and have been strongly associated with reported compliance rates (Steiner 1997). A medication possession ratio (MPR) measures the amount of therapy obtained over a specific period. For instance, a patient acquiring 90 days of therapy in a 180-day period would have an MPR of 0.5 (90/180), which means that the patient was compliant with his or her medication for 50 percent of the specific period (180 days). This MPR approach assumes:

- Patients should be on treatment for a given time period, (e.g., 180 days).
- Patients consumed all the medication they acquired.
- Patients are continuously eligible for the entire period of evaluation.

Patients then can be defined as being compliant or noncompliant with therapy, based on their MPR value. The HEDIS continuous compliance measure looks at a 231-day period and uses an MPR of approximately 80 percent, or 180 days of treatment over that period, as the definition of compliance with antidepressant therapy.

patients' quality of life, greatly reduced workplace productivity, unnecessary health care resource use, and poor clinical outcomes.

TURNING HEDIS AROUND: THE ROLES OF MAJOR STAKEHOLDERS

The physician's contribution

The majority of patients with depression is seen by PCPs; according to the literature, however, clinical outcomes of patients treated by psychiatrists are superior (Lin 1995, Simon 1993). There are several reasons for this. Depression is a common comorbidity of many chronic diseases; thus, the primary diagnosis may mask or confuse a secondary depression diagnosis. Additionally, depression's high unrecognized overlap with anxiety symptoms (60 to 90 percent) can make a definitive diagnosis difficult (Montgomery 2000). PCPs also can have difficulty diagnosing various types of anxiety, and they often simply categorize them as acute or persistent.

There is a relatively large body of published literature documenting the high rate of missed or incorrect diagnoses. For example, roughly half of psychiatric cases presenting in primary care go unrecognized, and one third of those cases that are recognized are misdiagnosed. According to one international expert, a correct diagnosis coupled with thoroughly appropriate treatment occurs in only about 5 percent of all cases (Lecrubier 2001). Other research teams put the rate of accurate diagnosis at 59 to 75 percent; although, when patients with GAD also were analyzed, their rate of accurate diagnosis was only 34 percent, and only a small percentage of the diagnosed patients were prescribed medications or referred to specialists (Wittchen 2001, 2002).

“There is a critical need for scripting discussion bullet points for PCPs and nurse practitioners to use in conversations with patients who are potentially suicidal. Seventy percent of all people who went on to commit suicide had met with their PCP within a month of their death. I believe the problem is that PCPs don't know the right questions to ask or how they can really help their patients.”

— JAY POMERANTZ, MD

There are several explanations as to why PCPs inadequately manage their patients with depression. PCPs might not fully understand the natural course of the disease (Kupfer 1991). Compared to psychiatrists, they may be less informed about diagnostic tools, medication choices, the accurate evaluation of clinical progress, and the role of other therapies. In addition, they might treat patients with depression or anxiety in the same way and might have difficulty in adapting evidence-based protocols to primary care (Kilbourne 2004). All these potential explanations have implications for compliance, duration of therapy, HEDIS scores, quality of care, and ultimately, cost (Sekula 2003).

“PCPs might hesitate to note a behavioral diagnosis in a medical chart because they are under the impression that they won't get paid for seeing those patients. PCPs are concerned that private MCOs and CMS [Centers for Medicare and Medicaid Services] discriminate against mental health diagnoses.”

— JAY POMERANTZ, MD

Employers and depression

Annually, depression and other mental health disorders result in millions of employee sick days, presenteeism (showing up for work but being only marginally productive), and short-term disability (NCQA 2004). In 2000, this translated into approximately 62 percent of all depression-related costs: a \$51.5 billion price tag for em-

ployers (Greenberg 2003). Despite this staggering figure, employers remain unconvinced of the cost-effectiveness of disease management programs. Although 53 percent of employers surveyed offer such programs to their employees with diabetes, only 31 percent offer those programs to employees with depression (Diamond 2004). Observational data suggest that the productivity gains that would follow from effective depression treatment could far exceed direct treatment costs, but randomized trials and formal cost-benefit research are necessary to determine which approach ultimately is cost effective for employers and other payers (Neumeier-Gromen 2004, Rost 2004, Schoenbaum 2001, Simon 2001).

“Employers say they understand the costs associated with anxiety and depression. MCOs have to frame their data analyses in a way that employers force them to. They have to think in terms of budgets and employee productivity. That’s not what we’re talking about, we’re talking about people.”

— WAYNE LEDNAR, MD, PHD

“Large employers have been bailing out the government by covering retirees, but that will not be the case in the future. Employers will start to follow the government’s lead as a result of the new MMA legislation, so it’s important that they play an active and responsible role.” — WAYNE LEDNAR, MD, PHD

Considering the gap in the published literature on the cost effectiveness of disease management programs for employees with mental health disorders, employers and other payers understandably have been committed to a low-cost approach. In practice, this becomes a generics-first strategy in the treatment of most chronic diseases, including depression and anxiety.

Managed care responds: generic step therapy programs

Many MCOs implement generic step therapy (GST) programs that require the use of generic selective serotonin reuptake inhibitors (SSRIs) before providers can prescribe branded products for depressed patients with or without comorbid anxiety. When evaluating pharmacy and administrative costs only, step therapy appears cost effective (Motheral 2004). For example, one MCO reported a \$3.4 million savings in pharmacy costs over a 6-year period while using generics-first, three-tier, or step-therapy strategies based on a 10,000 member plan (Cox 2004). Nevertheless, this analysis did not take into account overall medical costs, nor did it determine whether resource use increased in the ER, hospital, laboratory, medical office, or elsewhere within the system. This type of analysis still views costs in silos, with phar-

macy costs separated from overall medical costs.

Medicare Modernization Act, federal government, and antidepressants

In the senior population, depression and GAD are common but underestimated, undertreated, and poorly researched. In the elderly, GAD has the potential for negative outcomes independent of its common comorbidity with major depression (Alwahhabi 2003). Access to antidepressants is key to adequate treatment of this group. The Medicare Prescription Drug, Improvement, and Modernization Act (MMA), which becomes effective January 1, 2006, potentially will provide for an increase in the senior population’s access to antidepressants and other medically necessary prescription drugs.

Depending on how individual plans decide to structure their formularies, Part D of the MMA almost certainly will affect coverage for many persons on an antidepressant regimen. For example, under the new legislation, plans’ formularies will have to include at least two drugs within each therapeutic class, and one may be generic. The drugs within the class will have to be chemically distinct, not branded and generic equivalents or different dosages of the same brand. Medicare does not, however, require that plans offer branded and generic drugs the same unrestricted access.

For antidepressants, Medicare requires a plan’s formulary to include these classes:

- Monoamine oxidase (type A) inhibitors
- Reuptake inhibitors
- Other antidepressants such as bupropion, maprotiline, mirtazapine, and trazodone

Given that under the MMA legislation a plan must provide at least one branded antidepressant on its formulary, it is essential that patients and providers understand the potential differences in clinical benefits (safety, efficacy, and compliance) between available products. For those Medicare patients already doing well on a branded drug, MMA provides an exemptions and appeals process whereby patients may be “grandfathered” on their current medication, even if that medication is removed from the formulary when the MMA is enacted.

“The government needs to be more involved. We are likely to follow the lead of PBMs [pharmacy benefit managers], which makes them extremely important determinants of future health care expenditures. I believe that MMA will have a huge impact.”

— LEO SULLIVAN, RPH, DPH

Manufacturers still not convinced

Many patients discontinue SSRI therapy prematurely due to an adverse event (AE). Numerous published stud-

ies document rates of discontinuation and reasons for noncompliance with therapy. In one cohort of managed care patients (n=672), discontinuation or switching medications due to an AE occurred in 43 percent of depressed patients in the first 3 months and in 27 percent of patients in the next 3 months. The primary AE was fatigue, followed by treatment-emergent nausea, headache, and anxiety (Bull 2002). Compliance was found to improve, however, if patients were informed of potential AEs, and educated about the importance of the duration of therapy in achieving remission of symptoms and regaining functionality (Lin 1995).

Prescribing medications with a lower incidence of side effects might mitigate the need to change therapies, improve patient compliance, and reduce overall health care costs. This appears to be especially true for depressed patients with a comorbid anxiety disorder, as these patients demonstrate a particular sensitivity to the side effects of antidepressants. Eaddy and colleagues (2005) found that patients who required a therapy change (an augmentation or treatment switch) were more likely to be diagnosed with a comorbid anxiety disorder.

ANTIDEPRESSANT COMPLIANCE RATES AND HEALTH CARE RESOURCE CONSUMPTION

Early discontinuation of antidepressant therapy has adverse clinical, economic, and quality of life ramifications. Similar negative outcomes are due to switching therapies, augmenting therapies, and partial compliance. Measurement of these ramifications was the objective of the National Managed Care Depression and Anxiety Database (NMCD) Study, possibly the largest naturalistic retrospective database research ever conducted on depression and anxiety. The database, a subset of the PharMetrics Integrated Outcomes Database (Watertown, Mass.), is populated by 2 years of administrative claims data representing:

- 64 health plans and 38 million members
- 1.9 billion health care services
- Over 1 million patients prescribed antidepressants
- Patterns of treatment for these patients from 2001 to 2002

Analysis of phase 1 documented discontinuation rates among 740,199 members who had been prescribed immediate-release (IR) SSRIs for a diagnosis of depression. Percentages of discontinuation are illustrated in Figure 2.

These rates of discontinuation are similar to other published rates of discontinuation for patients on antidepressant regimens. With 72 percent of patients dropping out of ther-

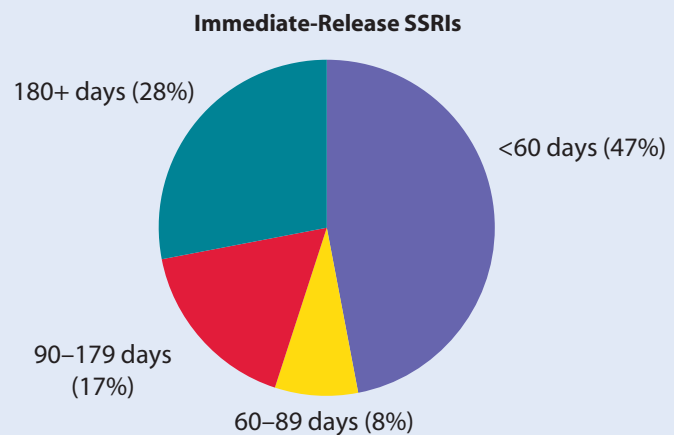
apy prior to 180 days, it is understandable that the national HEDIS performance indicators, which measure the effective continuation-phase adherence to antidepressant therapy, are so low.

In a phase 2 analysis of a subset of patients from the NMCD (n=65,753), Eaddy and colleagues measured costs associated with five observed medication scenarios:

- Discontinuing therapy in <90 days
- Medication compliance \geq 90 days
- Partial compliance, defined as patients on at least 90 days of continuous therapy with evidence of 1 or more 15-day gaps in therapy after 90 days
- Upward titration, defined as increasing dosage at some point during last 90 days of continuous treatment
- Therapy change, defined as patients either switching therapies or augmenting (adding another medication) during 90 days of continuous therapy

Total annual average health care charges were highest in patients who changed (switched or augmented) antidepressant therapy during the 18-month study period (\$10,969) and were lowest for those who remained on their initial therapy for longer than 90 days (\$7,453). The primary reason for this difference was inpatient costs; hospitalization costs for the patient cohort that changed therapy were the highest. Inpatient costs were lowest among those patients who had remained on therapy for longer than 90 days (Eaddy 2005). The results validate and confirm a seminal article by Thompson (1996) showing that therapies lasting longer than 90 days are the most cost effective, and that inpatient expenditures are

FIGURE 2 NMCD phase 1 results: member discontinuation



NMCD=National Managed Care Depression and Anxiety Database.
N=740,199.
SOURCE: EADDY 2003A

the most significant factor in overall treatment costs.

“When patterns of health care use are examined for patients with anxiety — who may or may not have depression as a comorbidity — the finding is that these patients are least compliant with antidepressant therapy. They use more health care resources than individuals who are diagnosed only with depression, and their SSRI change rates are highest when generics are prescribed.”
— DAVID SHEEHAN, MD, MBA

NATIONAL PHARMACOLOGICAL TRENDS IN THE TREATMENT OF ANXIETY DISORDERS

SSRIs are now recommended as the first line of therapy for the following: PTSD, panic disorder, GAD, social phobia/SAD, and OCD. This trend is accompanied by decreasing use of benzodiazepines and psychotherapy for the treatment of anxiety disorders (Olfson 2004). While benzodiazepines effectively relieve insomnia and agitation at treatment onset, there are drawbacks to their long-term use. These include:

- Daytime sedation
- Psychomotor impairment
- Dependence
- Risk of withdrawal syndrome on discontinuation
- Potential for drug-drug interactions (Bruce 2003)

Bupirone has some demonstrated efficacy in treating GAD, but it is not effective or indicated in the treatment of panic disorder or OCD. It has a slow (3- to 4-week) onset of action, and it has no clinically significant antidepressant effects (Ballenger 2000).

In the treatment of PTSD — a highly prevalent anxiety disorder that is frequently accompanied by suicidal behavior, impairment of daily functioning, and significant rates of comorbidity — only the SSRIs sertraline and paroxetine have been approved by the United States Food and Drug Administration. In the treatment of depression with associated anxiety, tricyclic antidepressants are similar in efficacy compared to SSRIs. Yet, SSRIs have superior safety and tolerability profiles and a more favorable AE profile (Asnis 2004, Montgomery 2000).

FIGURE 3 FDA approvals of commonly used antidepressants

	Depression	Panic disorder	OCD	SAD	GAD	PTSD
Paroxetine CR*/IR	×*	×*	×	×*	×	×
Sertraline	×	×	×	×		×
Fluoxetine	×	×	×			
Venlafaxine XR/IR	×			×	×	
Citalopram	×					
Fluvoxamine			×			
Escitalopram	×				×	

GAD=generalized anxiety disorder, OCD=obsessive-compulsive disorder, PTSD=post-traumatic stress disorder, SAD=social anxiety disorder.

SOURCE: MANUFACTURERS' PACKAGE INSERTS

FDA approval of certain SSRIs for the treatment of panic disorder, OCD, SAD, GAD, and PTSD, as well as the APA's practice guidelines for panic disorder strongly indicate that anxiety with or without comorbid depression is treated most effectively with certain SSRIs. Also, a growing number of published studies have shown that SSRIs used in treating anxiety disorders are associated with lower rates of health care resource use, especially ER visits and lab work. These findings indicate a potential to lower overall cost to the health plan or system and to lighten the social burden of disease (Grudzinski 2001).

Regarding treatment efficacy for anxiety disorders, SSRIs are not interchangeable, and many have different FDA-approved indications (Figure 3). For example, Lexapro (escitalopram) is indicated for treating depression and GAD. The FDA recently denied Lexapro's application for treatment of SAD and panic disorder, however. The FDA noted that though 1 of 2 pivotal clinical trials indicated Lexapro's efficacy in treatment of SAD, it "raised questions related to the reliability of patient data at one study center." Without data from both trials, study results failed to reach statistical significance (Steyer 2005).

THE CORE BENEFITS OF CONTROLLED-RELEASE PAROXETINE

As discussed above, the early discontinuation of antidepressant therapy has negative clinical and economic consequences. Antidepressants with enhanced tolerability and demonstrated efficacy have been demonstrated to increase the time that patients will remain on therapeutic regimens. Controlled-release paroxetine (Paxil CR) was developed to improve gastrointestinal tolerability, particularly to reduce treatment-emergent nausea. The controlled-release formulation delays release of paroxetine until the tablet has passed beyond the stom-

ach, after which the drug is released into the intestinal tract over the next 4 to 5 hours.

Paroxetine CR has been approved by the FDA for treating depression, panic disorder, premenstrual dysphoric disorder, and SAD. Two identical double-blind 12-week clinical trials in adult patients with MDD evaluated the efficacy and tolerability of paroxetine CR (n=212) vs. paroxetine IR (n=217) vs. placebo (n=211). Compared with placebo, both paroxetine CR and IR showed measurable efficacy in reducing the symptoms of depression as measured by the 17-item Hamilton D Rating Scale for Depression. As early as the first week of therapy, symptom reduction occurred in the CR cohort. At the study's end, response and remission rates were 61.2 percent and 44 percent for placebo, 72.9 percent and 52.5 percent for paroxetine IR, and 73.7 percent and 56.2 percent for paroxetine CR. Rates of reported nausea were 14 percent for CR and 23 percent for IR during the first week of therapy ($P \leq .05$). Dropouts due to AEs were similar in the placebo group and the CR group (Golden 2002).

Paroxetine CR also has demonstrated efficacy in three studies of patients with panic disorders, as well as one study of patients with SAD. In all the aforementioned pivotal trials, paroxetine CR demonstrated efficacy and good tolerability profiles. Only 11 percent of patients with panic disorders and 3 percent of those with SAD dropped out of the clinical trials due to AEs. (Bang 2004).

Published meta-analyses and data that were presented at the 2003 APA annual meeting were pooled to determine the discontinuation rates of the antidepressants that are commonly prescribed for depression and anxiety disorders. Figure 4 illustrates the dropout rates due

to adverse events for most of the common SSRIs vs. placebo.

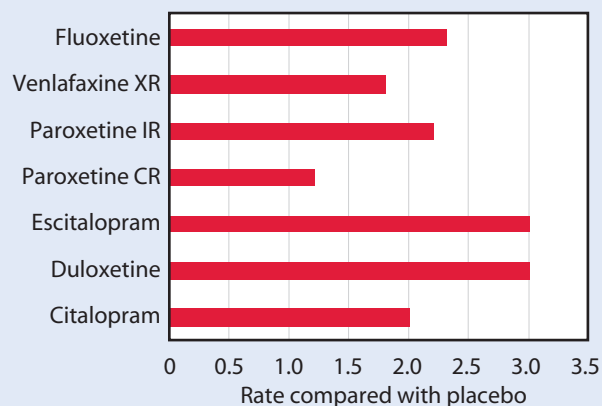
Analysis beyond clinical trial data

In a study comparing paroxetine CR with IR SSRIs, a survival analysis model was used to determine if the CR benefits seen in clinical trials would extend to longer durations of therapy in everyday practice settings. Survival analysis indicated that patients on the CR formulation would be 28 percent less likely to discontinue therapy compared to their IR counterparts during the 130-day time-to-treatment discontinuation analysis (Eaddy 2003b).

When this analysis was stratified by patients who had diagnosed depression (n=21,106), anxiety (n=16,741), and depression with comorbid anxiety (n=5,123), paroxetine CR demonstrated a respective 26 percent, 35 percent, and 31 percent reduction in the risk of discontinuing therapy compared to IR formulations (Regan 2003). In another retrospective database analysis, the study authors evaluated medication usage patterns among patients diagnosed with an anxiety disorder. In those prescribed an SSRI, the authors found fewer therapy changes for patients initially prescribed paroxetine CR compared to those on an IR regimen: a 30.8 percent chance of therapy change with paroxetine CR (the lowest rate of change) vs. a 43.9 percent of change with fluoxetine (Gdovin 2004).

The first study to directly compare the associated costs and discontinuation rates of paroxetine IR with paroxetine CR demonstrated that patients on a CR regimen (n=1,275) had a 40 percent reduction in the risk of discontinuation of therapy compared to patients in the IR cohort (n=2,550) when adherence to therapy was measured at 180 days. Additionally, when evaluating all medical charges such as inpatient, outpatient, physician visits, laboratory and medication costs, the CR cohort incurred \$119 less per month than IR-treated patients (Sheehan 2004).

FIGURE 4 Dropout rates due to adverse events vs. placebo in depression clinical trials



AE=adverse events.

Sertraline data not available.

SOURCES: NEMEROFF 2002, BEASLEY 2000, ST. LAMBERT 2003, GSK 2003

CONCLUSION

The differences in discontinuation and/or change rates found in the paroxetine CR studies do not necessarily establish a superior safety or efficacy profile. The definitive reasons for discontinuation and/or therapy change are unknown and could be related to factors other than tolerability. There is still a need for head-to-head placebo-controlled, randomized trials before absolute claims of superior cost-effectiveness, efficacy, and/or tolerability can be supported definitively. Before such

studies are completed, however, the published literature strongly supports trends that clinicians and policy makers should consider when making formulary choices and reviewing clinical practice guidelines for treatment of patients with depression and anxiety.

With the passage of the MMA, formulary components are especially important. This new legislation affords the possibility that seniors, as well as people with disabilities and low incomes, will have increased access to the medications they need and additional subsidies to pay for them. Therefore, it is incumbent on managed care decision makers and members of pharmacy and therapeutics committees to select formularies that are supported by proven efficacy in the treatment of depression and anxiety disorders. It is imperative that formulary choices for the treatment of depression and anxiety have good tolerability profiles, so that patients prescribed these medications will be as compliant as possible. Compliance with medication therapy translates to reduced use of health care resources and may prove to be cost-effective for plans, employers, and other payers.

Alignment of major stakeholders' interests will result in optimal care for patients with depression and anxiety. Passage of the MMA, broader dissemination of disease management program results, development of more efficacious and better-tolerated medications, continuation of vigorous randomized, controlled trials, and continued education on the association between length of therapy and improved clinical and economic outcomes also should contribute to better quality of care for these patients.

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