### **REPORTS**

## Anxiety Disorders in the 21st Century: Status, Challenges, Opportunities, and Comorbidity With Depression

C. Lindsay DeVane, PharmD; Evelyn Chiao, PharmD; Meg Franklin, PharmD; and Eric J. Kruep, PharmD, MS

#### **Abstract**

Anxiety disorders are highly prevalent in adults and often coexist with depression. Patients with anxiety commonly present to their primary care doctors, or in other medical settings, reflecting a high utilization of medical services. Furthermore, some patients initially complain of only somatic symptoms before they are ultimately diagnosed with a primary anxiety disorder. Approaches to management include both nondrug and drug treatments, and pharmacotherapy has substantial evidence-based support for efficacy. Of the drugs available for use, an antidepressant, and in particular a selective serotonin reuptake inhibitor, is the preferred initial treatment for most patients. This choice is based on the drug's proven efficacy, favorable adverse event profile, relative safety in overdose, and better management of comorbid depression. The treatment of anxiety disorders has multiple potential benefits in systems of managed care. These include the ability to maintain remission or prevent relapse, a decrease in comorbid depression, promotion of adherence with improvement in quality of life, and reduction in claims for medical care. This overview of the anxiety disorders sets the stage for subsequent discussions of managed care datasets highlighting the opportunities for making informed decisions about access to care and treatment that can lead to economic benefits, especially in light of the Medicare Modernization Act.

(Am J Manag Care. 2005;11:S344-S353)

his article describes the current burden of anxiety disorders and provides a synthesis of relevant findings in recent scientific literature to assist managed care decision makers in better understanding the importance and impact of anxiety disorders. The authors provide an overview of anxiety disorders with a focus on evidence-based medication management prin-

ciples in the general population. These comments should help provide insight into special challenges and opportunities in managed care populations. In light of the Medicare Modernization Act (MMA), special attention is focused on unique treatment considerations in the elderly. The remainder of this supplement presents important results from retrospective database studies conducted in large managed care settings. These studies were designed to provide decision makers and clinicians with real-world data to support anxiety and depression treatment decisions and offer a glimpse of what benefits may accrue in comparable treatment settings.

### **CURRENT STATUS**

#### **Epidemiology**

The lifetime prevalence of anxiety disorders is approximately 28.8% in the United States, with more than 1 of every 4 adults experiencing at least 1 anxiety disorder in their lifetime. Accordingly, anxiety disorders place a significant economic impact on the US healthcare system. The total annual cost of anxiety disorders has been estimated to be between \$42.3 billion and \$46.6 billion, of which more than 75% can be attributed to morbidity, mortality, lost productivity, and other indirect costs.<sup>2,3</sup> In comparison, the total economic burden of coronary artery disease may be as high as \$133.2 billion, whereas that of asthma may be as high as \$16.1 billion.4 Even more compelling is that the total cost estimate for

anxiety disorders comprises more than 30% of the total expenditures for mental illnesses; the cost of anxiety drug therapy accounts for 53% of the drug expenditures for mental illnesses.<sup>3,5</sup>

Of special significance to managed care organizations, a majority of frequent users of medical resources have symptoms of anxiety and/or depression. Schmitz and Kruse found that patients with a single anxiety disorder were 56% more likely to be a frequent user of medical services compared with patients with no anxiety disorder, and patients with comorbid anxiety and other psychiatric disorders were more than 3 times more likely to be a frequent user.<sup>6</sup> Remarkably, only 10% of frequent users with anxiety account for almost 30% of office visits, more than 50% of outpatient specialist visits, and 48% of days spent in a hospital.<sup>7</sup> Given the high resource consumption by this patient population and the significant economic impact they have on the healthcare system, further investigation is warranted into the most clinically appropriate yet cost-effective therapy for patients with significant anxiety and anxiety disorders.

### **Clinical Presentation of Anxiety Disorders**

The clinical manifestation of anxiety can vary widely from nonspecific somatic symptoms to severely debilitating illness. The diagnosis of chronic anxiety disorders can be difficult, because nonspecific or vague symptoms can be masked by other comorbid conditions or may be inadequately described or expressed by the patient. Physical symptoms, such as chest pain, fatigue, headache, insomnia, shortness of breath, dizziness, nausea, palpitations, and numbness, are often nonspecific and may mimic the patient's existing comorbid conditions,<sup>5</sup> further complicating the differential diagnosis of an anxiety disorder. Anxiety can also be triggered by underlying medical conditions, such as hypoparathyroidism, pheochromocytoma, or even coronary artery disease.8 Another common precipitant of symptoms of anxiety is the initiation or withdrawal of various drugs, including antipsychotics, corticosteroids, thyroid hormones, and stimulants.<sup>5</sup> Comorbidity with psychiatric disorders is common, especially major depressive disorder, but others include multiple anxiety disorders (panic disorder, social anxiety disorder [SAD], post-traumatic stress disorder [PTSD], generalized anxiety disorder [GAD]), and dementia. It is important to differentiate chronic anxiety disorders from acute anxiety triggered by life events or stressors or anxiety from other psychiatric conditions.

The majority of patients with anxiety disorder (83%) present to their physician with somatic symptoms, although studies have shown that physicians are less likely to recognize psychiatric illness if presented with physical symptoms alone.<sup>5,8</sup> However, the number of physical symptoms reported by the patient may be an indication of an anxiety disorder, with a higher number of symptoms being associated with a higher likelihood of an anxiety disorder.5 Other clues may also help distinguish anxiety disorders from underlying medical conditions. For instance, patients suddenly developing new-onset anxiety symptoms after the age of 35 who have otherwise been in good physical health with no previous symptoms of anxiety should be evaluated for underlying medical conditions. Generally, adult patients experiencing an anxiety disorder are likely to have had an anxious childhood or adolescence.8 Diagnosis of anxiety disorders can be further complicated if patients do not report symptoms associated with anxiety to their physician. This situation can occur when a patient feels there is a negative stigma associated with a mental disorder diagnosis.

Because of the difficulty in recognizing and properly diagnosing anxiety disorders, epidemiological prevalence rates may underestimate the true number of people experiencing an anxiety disorder, which is particularly true in the elderly. For example, Mulsant et al conducted a retrospective cohort study and found that one third to one half of elderly inpatient subjects had severe anxiety symptoms, whereas only 8% had a *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)*-diagnosed anxiety disorder. 10,11

### **Classification of Anxiety Disorders**

The term "anxiety disorder" encompasses 5 major disorders defined by the National Institutes of Mental Health. These are GAD,

Table 1. Major Types of Anxiety Disorders by NIMH Classification

Anxiety disorder	Lifetime prevalence*	Characteristics	
Social anxiety disorder	12.1% ± 0.4%	A fear of negative evaluation in social or performance situations, resulting in distress of functional impairment; distress may be generalized or specific $^{\dagger \ddagger}$	
Post-traumatic stress disorder	6.8% ± 0.4%	Persistent symptoms of anxiety which occur after an extremely traumatic or life-threatening event, persisting for at least 4 weeks; patients often relive the triggering event $^{\dagger\$}$	
Generalized anxiety disorder	5.7% ± 0.3%	Pervasive and uncontrollable worrying and anxious feelings that persist for at least 6 months, accompanied by at least 3 of the following: restlessness, difficulty concentrating, easy fatigability, irritability, muscle tension, disturbed sleep† <sup>S  </sup>	
Panic disorder	4.7% ± 0.2%	Recurring panic attacks (sudden and unprovoked episodes of fear and discomfort), which may be accompanied by somatic symptoms, such as palpitations, increased heart rate, chest pain, nausea, trembling, shortness of breath, or sweating <sup>†§</sup>	
Obsessive-compulsive disorder	1.6% ± 0.3%	Uncontrollable obsessive thoughts (obsessions) and feelings that result in ritualistic actions (compulsions) that may relieve symptoms of anxiety $^{\dagger}$ ¶	

NIMH indicates National Institutes of Mental Health.

obsessive-compulsive disorder (OCD), panic disorder, phobias, including SAD, and PTSD. <sup>12</sup> Additional subtypes are identified by the *DSM-IV*. <sup>13</sup> The most common anxiety disorders are SAD (lifetime prevalence 12.1%), PTSD (6.8%), and GAD (5.7%). <sup>1,14</sup> A brief description of the 5 major anxiety disorders is provided in **Table 1**.

#### **Comorbid Anxiety and Depression**

Comorbid anxiety disorders and major depressive disorder (depression) are frequently encountered concurrently; an estimated 85% of patients with depression have symptoms of anxiety, and 58% have a diagnosis for an anxiety disorder during their lifetime. The prevalence of comorbid GAD and depression, the most common combination, has been reported in as high as 60% to 90% of patients with GAD in community

populations.<sup>9</sup> Comorbid anxiety and depression is especially common in the elderly<sup>18</sup> and has been associated with significantly greater severity of somatic symptoms and significantly poorer social functioning compared with elderly patients with depression alone.<sup>11</sup> These patients also tend to have lower Global Assessment Scale scores and more severe symptoms of depression.<sup>11</sup> Additionally, patients with comorbid conditions are more frequent users of medical resources, as demonstrated by Sheehan et al in this supplement and others.<sup>6,19</sup>

#### APPROACHES TO TREATMENT

#### **Drug and Nondrug Treatment**

In general, 2 types of treatment are available for anxiety disorders—psychotherapy

<sup>\*</sup>Source: Reference 1.

<sup>†</sup>Source: Reference 14.

<sup>‡</sup>Source: Reference 15.

<sup>§</sup>Source: Reference 5.

<sup>||</sup> Source: Reference 16.

<sup>¶</sup> Source: Reference 17.

and pharmacotherapy. One or both approaches can be effective depending on the specific anxiety disorder being treated. Psychotherapy, which includes cognitive behavioral therapy (CBT) and collaborative care, has been effective for specific phobias, whereas pharmacotherapy alone or in combination with psychotherapy is generally considered the treatment standard for most anxiety disorders. CBT involves training patients to recognize internal or external stimuli that are associated with feelings of anxiety, altering maladaptive patterns of response to such stimuli, thus allowing patients to reduce their anxiety. Collaborative care, a method of disease management that involves close collaboration between the patient, primary care provider, and behavioral care specialist, has been shown to improve the quality of care and clinical outcomes in certain anxiety disorders, such as panic disorder, although studies are conflicting. 20,21

Pharmacotherapy treatment algorithms for anxiety disorders vary based on the specific diagnosis. Anxiolytic agents, of which benzodiazepines and buspirone are the principal members, may be used for acute anxiety relief for a limited period, but, in general, patients should begin treatment for chronic anxiety disorder with an antidepres-

sant (either a selective serotonin reuptake inhibitor [SSRI] or a mixed-mechanism antidepressant). A summary of the most recent consensus treatment guidelines is found in **Table 2**.

Anxiolytics. Anxiolytics have historically been the mainstay of treatment for anxiety disorders. Given their relatively high side effect burden and inconsistent results in reducing symptoms or inducing remission, these agents are no longer recommended as first-line treatment.

Benzodiazepines have been the most widely studied and utilized class of drugs for anxiety disorders and were the treatment of choice for many years. 15,16 Their efficacy in reducing somatic symptoms has been documented, but they produce little improvement in the psychic symptoms of anxiety and have questionable efficacy in long-term treatment; studies have shown a reduction in Hamilton Anxiety Scale scores similar to placebo.<sup>23</sup> Additionally, benzodiazepines are associated with a higher burden of central nervous system side effects, such as cognitive impairment, psychomotor impairment, and daytime sedation, than other therapeutic options, 11 as well as a risk of dependence and producing a discontinuation syndrome.<sup>22,24</sup>

Table 2. Summary of Recent Guidelines for Treatment of Anxiety Disorders

Anxiety disorder	Expert panel	Summary of recommendations	Recommended minimum duration of therapy
Panic disorder	APA	CBT or pharmacotherapy	12 to 18 months
	ICGDA	SSRIs	12 to 24 months
GAD	ICGDA	SSRIs, SNRIs, TCA, and CBT	12 months to lifelong*
SAD	ICGDA	SSRIs	12 months
PTSD	ICGDA	SSRIs, CBT	12 to 24 months
OCD	Expert consensus for OCD, AACAP	CBT or SSRIs $\pm$ clomipramine CBT $\pm$ SSRIs	12 to 24 months 12 to 18 months

APA indicates American Psychiatric Association; ICGDA, International Consensus Group on Depression and Anxiety; AACAP, American Academy of Child and Adolescent Psychiatry; GAD, generalized anxiety disorder; SAD, social anxiety disorder; PTSD, post-traumatic stress disorder; OCD, obsessive-compulsive disorder; CBT, cognitive behavioral therapy; SSRIs, selective serotonin reuptake inhibitors; SNRI, serotonin norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.

\*Source: Reference 10.

Source: Adapted from Reference 22, except where noted.

The negative effects of benzodiazepines may be increased significantly in the elderly. Elderly patients demonstrate impaired pharmacokinetics for a variety of drugs.<sup>25</sup> This population has a slowed drug metabolism compared with younger adults due to decreases in the activity of hepatic cytochrome P450 enzymes that metabolize these drugs.<sup>26</sup> The elimination half-life of a benzodiazepine, such as diazepam, may be increased 4- to 5-fold, increasing the severity and duration of side effects. 27 Although some controversy remains, benzodiazepines have been repeatedly associated with a risk of hip fractures in the elderly.<sup>28,29</sup> Elderly patients receiving long-term benzodiazepines have a significantly higher risk of decline on cognitive function tests over a 4year period than nonusers.30 For instance, benzodiazepines have been shown to be a risk factor for cognitive impairment in the elderly. Long-term users of benzodiazepines had a significantly higher risk of cognitive decline in the global cognitive test (Mini Mental State Examination) than nonusers.<sup>30</sup>

Because of these risks, benzodiazepines are not recommended as the mainstay of therapy and should be limited to only the acute phase of anxiety treatment for up to 2 to 4 weeks or to manage breakthrough symptoms during the initiation of an anti-depressant or other long-term therapy.<sup>31</sup> The continued use of benzodiazepines in patients who show no response after 2 weeks is contraindicated.<sup>31</sup>

**Table 3.** SSRI FDA-approved Indications for Anxiety Disorders

SSRI agent	FDA-approved anxiety indication	
Fluoxetine/Fluoxetine weekly	OCD, PD (weekly, not approved for anxiety)	
Sertraline	OCD, PD, PTSD, SAD	
Paroxetine IR/Paroxetine CR*	OCD, PD,* SAD,* GAD, PTSD	
Citalopram	No approval for anxiety	
Escitalopram	GAD	
Fluvoxamine	OCD	

<sup>\*</sup>Indications for which paroxetine CR is approved.

SSRI indicates selective serotonin reuptake inhibitor; FDA, US Food and Drug Administration; OCD, obsessive-compulsive disorder; PD, panic disorder; PTSD, post-traumatic stress disorder; SAD, social anxiety disorder; IR, immediate release; CR, controlled release; GAD, generalized anxiety disorder.

Buspirone, a 5-HT<sub>1A</sub> partial agonist, is another anxiolytic historically used in anxiety. Buspirone has only been shown to be effective in GAD and comparable with placebo in acute anxiety and panic disorder, but does have an improved tolerability profile and decreased drug interactions compared with benzodiazepines. Like benzodiazepines, however, buspirone is not effective in managing symptoms of depression that are frequently comorbid in patients with GAD. The relative complexity of a buspirone regimen (multiple daily dosing) increases the risk of nonadherence and makes it less favorable as primary therapy.

**Antidepressants.** More recently, practice patterns have shifted to the antidepressant class as the most commonly prescribed for anxiety disorders. This is due to their proven efficacy in anxiety as well as in commonly comorbid depressive symptoms. Although efficacy between the SSRIs and the tricyclic antidepressants (TCAs) is similar, the SSRIs have an enhanced safety and tolerability profile, making them the preferred agent for all anxiety disorders.<sup>22</sup> The considerable side effect burden, the possibility of producing anticholinergic delirium, and their contribution to promoting falls and hip fractures, make TCAs especially unsuitable for the elderly and no longer recommended.

SSRIs have been proved to relieve many of the anxiety and/or depressive symptoms associated with anxiety disorders, such as GAD, SAD, panic disorder, OCD, and PTSD. They are effective, well tolerated, and relatively safe in overdose situations, making them an ideal choice for the treatment of anxiety, particularly for the elderly population.<sup>32,33</sup> Although the majority of SSRIs have gained US Food and Drug Administration (FDA) approval for major depressive disorder, they may not be interchangeable in the treatment of anxiety disorders, because each SSRI has different FDA approvals for the anxiety disorders (Table 3). For example, a recent request to extend escitalopram's indications to SAD and panic disorder was recently denied by the FDA,34 citing lack of efficacy. In addition to efficacy differences, dissimilarities in tolerability have also been described and may be the leading cause of

therapy change and patient nonadherence with many of the immediate-release SSRIs, especially in patients with anxiety disorders with or without comorbid depression.<sup>35</sup>

Other Agents. Venlafaxine and extended-release venlafaxine are antidepressant agents that have also shown efficacy in treating anxiety disorders. Classified as serotonin norepinephrine reuptake inhibitors, they are generally well tolerated and have been effective in the treatment of GAD, panic disorder, and SAD.<sup>5</sup> The efficacy of venlafaxine has been maintained during long-term treatment courses. The side effect profile for venlafaxine includes nausea, dizziness, somnolence, and dry mouth; however, these events usually decline with long-term use of the agent.<sup>36</sup>

Monoamine oxidase inhibitors (MAOIs) have been shown to be effective in relieving anxiety in some patients; however, these drugs have significant drug interactions and a high side-effect burden. The dietary restrictions necessary for use of an oral MAOI<sup>37</sup> make these drugs a poor treatment option, particularly in the elderly.<sup>5</sup>

As seen in Table 2, regardless of the type of anxiety disorder, treatment should be maintained for at least 12 months, highlighting the fact that anxiety disorders, like depression, tend to relapse and remit, and long-term, continuous treatment should be started to prevent relapse. Even with longterm therapy, less than 50% of patients with GAD have achieved full remission after 5 years, and of patients with full or partial remission, 27% and 39%, respectively, relapsed within 3 years.<sup>38</sup> The nature and cause of high rates of relapse have not been fully investigated, but possible factors are comorbid disorders, poor adherence, and the initial choice of an anti-anxiety agent. Work by Melfi et al and Claxton et al, for example, have demonstrated a significantly increased risk of relapse of depression in patients who are only partially adherent with antidepressant therapy or discontinue therapy early compared with those who are adherent for a minimum duration. 39,40 Similarly, Eaddy et al clearly demonstrate the relationship between treatment duration and

all-cause hospitalizations in depression, finding a 14% reduced risk of all-cause hospitalization for every 30-day increase in antidepressant treatment duration up to 90 days. 41

Thus, the key issues regarding pharmacotherapy for anxiety disorders are efficacy, safety, and the ability to maintain remission or prevent relapse. However, drug treatment is only effective when it is taken appropriately, therefore, factors such as tolerability and enhanced adherence profile have a significant impact on a drug's ability to maintain remission or prevent relapse. These factors are clearly not equivalent between the classes of medications or within the drug classes. Previous work has demonstrated that tolerability, and subsequently adherence, among the SSRI class is not equivalent.35,42 Retrospective claims analyses in large commercial managed care datasets have found that improved adherence has also been associated with reduced medical costs, 43,44 primarily thought to be driven by a reduction in acute medical care required for relapse in depression. Additional comparative SSRI adherence and economic results are presented in this supplement.

## CHALLENGES

# **Special Populations: Comorbid Anxiety and Depression**

Patients presenting with depression and comorbid anxiety disorders offer a special challenge in treatment, because they often have more severe clinical outcomes and require additional or more intense management; older depressed patients with symptoms of GAD have a worse outcome than those without anxiety. 45 Avoiding the use of an agent that may potentially worsen either condition or may lead to greater risk of relapse and poor outcomes are important treatment considerations in this comorbid population. Benzodiazepines are not included in the American Psychiatric Association's guidelines for treatment of major depressive disorder and should not be used in anxiety patients with comorbid depression. An agent that is effective and tolerable for both disorders is the most desirable. Pertaining to this

very prevalent and challenging mental health comorbidity, additional adherence and economic data differentiating the available SSRIs are featured in this supplement.

#### **Special Populations: The Elderly**

Considering the ever-increasing number of patients eligible for Medicare, expected to near 80 million enrollees in 2030, and the anticipated coverage of prescription drugs under the MMA in 2006, treatment considerations for anxiety disorders in the elderly deserve special attention. Anxiety disorders and comorbid anxiety and depression, although not as prevalent as in a younger population, are still common among the elderly; prevalence estimates have ranged from 14% to 17%. 46,47 The presence of anxiety disorders has also been associated with an 87% greater risk of mortality over 7 years in elderly men compared with elderly men without anxiety, which may be due to an increased sensitivity to the autonomic activity induced by symptoms of anxiety or psychosocial implications, such as stress-related cardiovascular dysfunction or suicidal ideology. 47

Given the heightened sensitivity to anxiety that may be present in the elderly and understanding that the elderly may also be more sensitive to medication effects, such as an increased sensitivity to anticholinergic effects, careful attention should be given to treating psychiatric disorders in this population. The Beers criteria, initially published in 1991, provide guidelines and recommendations for medications that should not be prescribed to the elderly in a nursing home setting. The criteria have since been applied to a variety of settings and have been recently updated to include medications that generally should be avoided in elderly patients, regardless of the setting.<sup>48</sup> Included on the most updated criteria are long-acting benzodiazepines, independent of diagnosis or conditions.<sup>48</sup> Even though benzodiazepines are considered an inappropriate therapy for use in the elderly, they are the most frequently prescribed anti-anxiety agents in the elderly. 27,49,50 Although benzodiazepines are efficacious with regards to acute anxiety and onset,<sup>51</sup> side effects, such as sedation, drowsiness, and central nervous system depression, have been linked to cognitive dysfunction, falls, immobility, and hip fractures in the elderly.<sup>52</sup> The long-acting benzodiazepines or those prescribed at higher than recommended doses pose an even greater risk to the elderly population because of a reduced capacity for hepatic or renal clearance of drugs.<sup>27,53</sup>

Of particular interest to health plans, the National Committee for Quality Assurance introduced a new measure on drugs to be avoided in the elderly to the 2006 Health Employer Data and Information Set (HEDIS). The measure evaluates the frequency of inappropriate drug utilization in Medicare members, of which the long-acting benzodiazepines are included.<sup>54</sup> Similarly, the Centers for Medicare and Medicaid Services (CMS) have declared that the benzodiazepines will not be covered under Medicare's new prescription program, Part D, of the MMA.<sup>55</sup> As such, SSRIs will likely become the primary agents used in this population. With the introduction of newer SSRIs and the number of SSRIs that are available generically, clinicians must continue to evaluate which SSRI provides the highest likelihood of therapeutic success in elderly patients with anxiety disorders. Recent evidence,35 along with additional research presented in this supplement, may provide managed care decision makers with important data differentiating among the available SSRIs in treating depression and/or anxiety disorders in the elderly population.

## OPPORTUNITIES

Although the elderly present a unique set of challenges in treatment of anxiety and depression, managed care decision makers will have multiple opportunities to provide quality, cost-effective care in this population. For example, the MMA will provide access to prescription medications for millions of Medicare beneficiaries who had no coverage before, considerably expanding the treatable population. In addition to CMS, the prescription drug program will also be managed by private managed care companies through stand-alone prescription drug plans or Medicare Advantage plans, which replace

the traditional Medicare+Choice program. As such, health plans will face a growing number of members seeking treatment for anxiety and depression. This presents an opportunity for plan decision makers to enhance care in elderly populations for a greater number of patients through targeted quality improvement initiatives, such as those seen in the HEDIS 2006 measures in the elderly (eg, improving adherence to pharmacotherapy or decreasing inappropriate therapy).

The development of drug formularies unique to each plan sponsor, mandated by the MMA, clearly also has implications for managed care decision makers. The MMA requires a minimum of 2 chemically distinct drugs in each therapeutic class for the formulary but does not limit the number of covered agents or mandate open access. This presents an opportunity for decision makers to develop a cost-effective drug formulary for anxiety and depressive disorders while providing good clinical outcomes. As has been discussed above, therapy should not only address efficacy but should also address patient-level issues, such as tolerability and adherence. There is a need, then, to differentiate the therapeutic alternatives, because these issues are not equivalent across the agents. In this supplement, Keene et al demonstrate adherence differences among the SSRIs in a treated elderly population,<sup>56</sup> whereas Sheehan et al present the economic differences among these agents.<sup>19</sup>

Managed care decision makers also have the opportunity to affect provider and patient treatment decisions through widespread implementation of their own drug benefit policies. However, careful and informed consideration should go into formulary design or policy implementation to provide the best quality of care. As Panzer et al demonstrate in this supplement through an economic impact model, SSRIs do not result in similar treatment outcomes, but ultimately result in an overall cost increase rather than a cost savings from a generic step therapy program.<sup>57</sup> Clearly, the initial choice of therapy in the treatment of patients with anxiety and depression may affect the need for therapy change, early treatment discontinuation, or other less desired medication utilization patterns. Therefore, considerations for a prescription plan design should account not only for drug cost but also for clinical efficacy, safety and tolerability, and effects on adherence, as these all significantly impact treatment success in patients with anxiety disorders and/or depression.

## SUMMARY

Anxiety disorders are prevalent in the United States in both a younger population and in the elderly. These disorders encompass a number of conditions with various symptomatologies and, as such, are often undiagnosed or misdiagnosed and undertreated. SSRIs are recommended as a firstline treatment in the pharmacological management of anxiety disorders due to their proven efficacy, safety and tolerability, and effectiveness in both anxiety disorders and commonly comorbid depression. Correctly identifying a patient's anxiety disorder and choosing an appropriate initial therapy with proven outcomes and improved patient-related factors is essential in the management of these disorders. With the implementation of the MMA, treating the elderly with anxiety disorders and/or depression appropriately will continue to be a challenge, but also an opportunity, for managed care plans. This supplement will provide managed care decision makers and clinicians with real-world data to support anxiety and depression treatment and policy decisions.

#### REFERENCES

- 1. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62:593-602.
- **2. Greenberg PE, Sisitsky T, Kessler RC, et al.** The economic burden of anxiety disorders in the 1990s. *J Clin Psychiatry.* 1999;60:427-435.
- **3. DuPont RL, Rice DP, Miller LS, Shiraki SS, Rowland CR, Harwood HJ.** Economic costs of anxiety disorders. *Anxiety.* 1996;2:167-172.
- **4. National Heart, Lung, and Blood Institute.** *Morbidity and Mortality: 2002 Chart Book on Cardiovascular, Lung, and Blood Diseases.* Bethesda, Md: National In-

- stitutes of Health, US Dept of Health and Human Services; 2004.
- **5. Arikian SR, Gorman JM.** A review of the diagnosis, pharmacologic treatment, and economic aspects of anxiety disorders. *Primary Care Companion J Clin Psychiatry*. 2001;3:110-117.
- **6. Schmitz N, Kruse J.** The relationship between mental disorders and medical service utilization in a representative community sample. *Soc Psychiatry Psychiatr Epidemiol.* 2002;37:380-386.
- **7. Katon W.** Panic disorder: relationship to high medical utilization, unexplained physical symptoms, and medical costs. *J Clin Psychiatry*. 1996;57(suppl 10):11-18.
- **8. Culpepper L.** Use of algorithms to treat anxiety in primary care. *J Clin Psychiatry*. 2003;64(suppl 2):30-33.
- **9. Flint A.** Generalized anxiety disorder in elderly patients: epidemiology, diagnosis and treatment options. *Drugs Aging.* 2005;22:101-114.
- **10.** Mulsant BH, Reynolds CF 3rd, Shear MK, Sweet RA, Miller M. Comorbid anxiety disorders in late-life depression. *Anxiety*. 1996;2:242-247.
- **11. Lenze EJ, Mulsant BH, Shear MK, et al.** Comorbid anxiety disorders in depressed elderly patients. *Am J Psychiatry*. 2000;157:722-728.
- **12. National Institute of Mental Health.** Facts about anxiety disorders. Available at: http://www.nimh.nih.gov/publicat/adfacts.cfm. Accessed September 6, 2005.
- **13. American Psychiatric Association.** Anxiety disorders. In: *Diagnostic and Statistical Manual of Mental Disorders.* 4th edition. Washington, DC: American Psychiatric Association; 2000:429-484.
- **14. Stein MB.** Attending to anxiety disorders in primary care. *J Clin Psychiatry*. 2003;64(suppl 15):35-39.
- **15. Blanco C, Raza MS, Schneier FR, Liebowitz MR.** The evidence-based pharmacological treatment of social anxiety disorder. *Int J Neuropsychopharmacol.* 2003;6: 427-442.
- **16. Sramek JJ, Zarotsky V, Cutler NR.** Generalised anxiety disorder: treatment options. *Drugs.* 2002;62:1635-1648.
- **17. Khonzam HR.** Obsessive-compulsive disorder: what to do if you recognize baffling behavior. *Postgrad Med.* 1999;106:133-141.
- **18. Beekman AT, de Beurs E, van Balkom AJ, Deeg DJ, van Dyck R, van Tilburg W.** Anxiety and depression in later life: co-occurrence and communality of risk factors. *Am J Psychiatry*. 2000;157:89-95.
- **19. Sheehan DV, Eaddy M, Shah MB, Mauch RP.** Differences in total medical costs across the SSRIs for the treatment of depression and anxiety. *Am J Manag Care*. 2005;11:S354-S361.
- **20. Roy-Byrne PP, Katon W, Cowley DS, Russo J.** A randomized effectiveness trial of collaborative care for patients with panic disorder in primary care. *Arch Gen Psychiatry*. 2001;58:869-876.
- **21. Roy-Byrne PP, Craske MG, Stein MB, et al.** A randomized effectiveness trial of cognitive behavior therapy and medication for primary care panic disorder. *Arch Gen Psychiatry.* 2005;62:290-298.
- **22. Bandelow B, Zohar J, Hollander E, et al.** World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders. *World J Biol Psychiatry*. 2002;3:171-199.
- **23. Rouillon F.** Long term therapy of generalized anxiety disorder. *Eur Psychiatry*. 2004;19:96-101.
- 24. Rickels K, Schweizer E, Case WG, Greenblatt DJ.

- Long-term therapeutic use of benzodiazepines. I. Effects of abrupt discontinuation. *Arch Gen Psychiatry*. 1990;47:899-907.
- **25. DeVane CL, Pollock BG.** Pharmacokinetic considerations of antidepressant use in the elderly. *J Clin Psychiatry*. 1999;60(suppl 20):38-44.
- **26.** Sotaniemi EA, Arranto AJ, Pelkonen O, Pasanen M. Age and cytochrome P450-linked drug metabolism in humans: an analysis of 226 subjects with equal histopathologic conditions. *Clin Pharmacol Ther.* 1997;61:331-339.
- **27. Chutka DS, Takahashi PY, Hoel RW.** Inappropriate medications for elderly patients. *Mayo Clin Proc.* 2004;79: 122-139.
- **28.** Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. Study of the Osteoporotic Fractures Research Group. *N Engl J Med*. 1995;332:767-773.
- **29. Ray WA, Griffin MR, Downey W.** Benzodiazepines of long and short elimination half-life and the risk of hip fracture. *JAMA*. 1989;262:3303-3307.
- **30. Paterniti S, DuFouil C, Alperovitch A.** Long-term benzodiazepine use and cognitive decline in the elderly: the Epidemiology of Vascular Aging Study. *J Clin Psychopharmacol.* 2002;22:285-293.
- **31. Rickels K, Rynn M.** Pharmacotherapy of generalized anxiety disorder. *J Clin Psychiatry*. 2002;63(suppl 14): 9-16
- **32. Lauderdale SA, Sheikh JI.** Anxiety disorders in older adults. *Clin Geriatr Med.* 2003;19:721-741.
- **33. Lader M.** Treatment of anxiety. *BMJ.* 1994;309: 321-324.
- **34. Steyer R.** FDA rejects expanding Lexapro marketing. Available at: http://www.thestreet.com/mktwrm/stocks/biotech/10215442.html. Accessed August 15, 2005.
- **35. Eaddy M, Bramley T, Regan T.** Time to antidepressant discontinuation: a comparison of controlled-release paroxetine and immediate-release selective serotonin reuptake inhibitors. *Manag Care Interface*. 2003;16: 22-27
- **36. Gorman JM.** Treatment of generalized anxiety disorder. *J Clin Psychiatry*. 2002;63(suppl 8):17-23.
- **37. Sweet RA, Brown EJ, Heimberg RG, et al.** Monoamine oxidase inhibitor dietary restrictions: what are we asking patients to give up? *J Clin Psychiatry*. 1995;56:196-201.
- **38.** Yonkers KA, Dyck IR, Warshaw M, Keller MB. Factors predicting the clinical course of generalised anxiety disorder. *Br J Psychiatry*. 2000;176:544-549.
- **39. Melfi CA, Chawla AJ, Croghan TW, Hanna MP, Kennedy S, Sredl K.** The effects of adherence to antidepressant treatment guidelines on relapse and recurrence of depression. *Arch Gen Psych.* 1998;55:1128-1132.
- **40. Claxton AJ, Li Z, McKendrick J.** Selective serotonin reuptake inhibitor treatment in the UK: risk of relapse or recurrence of depression. *Br J Psychiatry.* 2000;177: 163-168.
- **41. Eaddy M, Sarnes M, Regan T, Mauch R.** Examining the relationship between length of selective serotonin reuptake inhibitor treatment and the risk of hospitalization in a naturalistic managed care setting. Poster presented at: the Academy of Managed Care Pharmacy Educational Conference; Baltimore, Md; October 13-16, 2004.
- **42. DeVane CL.** Immediate-release versus conrolled-release formulations: pharmacokinetics of newer antidepressants in relation to nausea. *J Clin Psychiatry*. 2003;64(suppl 18):14-19.

#### Anxiety Disorders in the 21st Century: Status, Challenges, Opportunities, and Comorbidity With Depression

- **43.** Thompson D, Buesching D, Gregor KJ, et al. Patterns of antidepressant use and their relation to costs of care. *Am J Manag Care*. 1996;2:1239-1246.
- **44. Eaddy MT, Druss BG, Sarnes MW, Regan TS, Frankum LE.** Relationship of total health care charges to selective serotonin reuptake inhibitor utilization patterns including the length of antidepressant therapy—results from a managed care administrative claims database. *J Manag Care Pharm.* 2005;11:145-150.
- **45. Steffens DC, McQuoid DR.** Impact of symptoms of generalized anxiety disorder on the course of late-life depression. *Am J Geriatr Psychiatry*. 2005;13:40-47.
- **46. Ritchie K, Artero S, Beluche I, et al.** Prevalence of DSM-IV psychiatric disorder in the French elderly population. *Br J Psychiatry*. 2004;184:147-152.
- **47. van Hout HP, Beekman AT, de Beurs E, et al.** Anxiety and the risk of death in older men and women. *Br J Psychiatry.* 2004;185:399-404.
- **48.** Curtis LH, Ostbye T, Sendersky V, et al. Inappropriate prescribing for elderly Americans in a large outpatient population. *Arch Intern Med.* 2004;164:1621-1625.
- **49. Madhusoodanan S, Bogunovic OJ.** Safety of benzodiazepines in the geriatric population. *Expert Opin Drug Saf.* 2004;3:485-493.
- **50. Petrovic M, Mariman A, Warie H, Afschrift M, Pevernagie D.** Is there a rationale for prescription of benzodiazepines in the elderly? Review of the literature. *Acta Clin Belg.* 2003;58:27-36.

- **51. Ashton H.** Guidelines for the rational use of benzo-diazepines. When and what to use. *Drugs.* 1994;48: 25-40.
- **52. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH.** Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. *Arch Intern Med.* 2003;163:2716-2724.
- **53. Mort JR, Aparasu RR.** Prescribing of psychotropics in the elderly: why is it so often inappropriate. *CNS Drugs*. 2002;16:99-109.
- **54.** National Committee for Quality Assurance. Health Plan Employer Data and Information Set (HEDIS) 2006 Volume 2, Technical Specifications. 170-172.
- **55.** Centers for Medicare and Medicaid Services (CMS). The Medicare Prescription Drug, Improvement, and Modernization Act of 2003. Available at: www.cms.hhs.gov/medicarereform/MMActFullText.pdf. Accessed August 10, 2005.
- **56. Keene MS, Eaddy M, Nelson WW, Sarnes M.** Adherence to paroxetine CR compared with paroxetine IR in a Medicare-eligible population with anxiety disorders. *Am J Manag Care.* 2005;11:S362-S369.
- **57. Panzer PE, Regan TS, Chiao E, et al.** Implications of an SSRI generic step therapy pharmacy benefit design: an economic model in anxiety disorders. *Am J Manag Care.* 2005;11:S370-S379.