Current Psychiatry

CASES THAT TEST YOUR SKILLS

Anxious as a boy, Mr. A developed compulsions that were relieved by psychotherapy. Still he kept worrying—about his job, his wife, his concern that he had cancer and AIDS. Finally, he sought psychiatric help when …

At age 44 and physically fit, he feared imminent death

William P. Carter, MD
Instructor in psychiatry, Harvard Medical School, Boston, Mass

History Learning to worry

Mr. A, 54, is a hotel manager who has struggled with anxiety since childhood. At that time, he suffered primarily from incessant worries. Even then, he knew that his concerns were irrational, but he could not suppress them. Mild illness stirred up thoughts of his own death and then even the possibility of his parents' death. Water coming from a tap evoked images of disasters from a future global water shortage.

In the classroom, his elaborate concerns about his teachers' evaluations of him paralyzed him emotionally. While trying to manage this inner turmoil, even his obvious intelligence could not compensate for his time off-task in school, and a subsequent decline in his grades brought about the scrutiny he had dreaded, further exacerbating his anxiety.

By his teenage years, Mr. A developed classic compulsions, such as checking locks and engaging in counting rituals. In his 20s, he also found himself repeatedly returning home to confirm that he had turned off appliances. Over time, the doubt intrinsic to these compulsions only grew, and ultimately the associated anxiety became unbearable. Mr. A turned to increased alcohol use and even a brief experiment with heroin.

After self-medication brought no relief, Mr. A finally sought professional treatment at age 26. Although the compulsions caused the greatest burden, they were the most readily treated symptoms. His behavior-based psychotherapy led to full remission of his most overt symptoms. This treatment also helped alleviate some of his more circumscribed obsessions, but the diffuse worry proved to be more intractable.

After psychotherapy, just as in his childhood, Mr. A still worried about an ever-changing array of subjects. He worried about finances, his own physical health, and his wife's well being. He worried about his relationship with his customers, as well as his supervisor's assessment of him. Any physical symptom set off fears that he had can-

cer. In response to his memory of engaging in low-risk sexual behaviors in his distant past, he struggled to resist thoughts that he had AIDS. He stayed in excellent physical condition, combining strength training with 6 hours of aerobic exercise weekly. Still, he could not escape the nearly constant fear that his death was imminent.

In your view, what single diagnosis best explains Mr. A's symptoms? What other conditions are you considering—or would you have considered earlier in his life?

Dr. Carter's observations The childhood history highlights a major controversy: psychiatric treatment of inattentive children who are not performing well in school. We psychiatrists are accused of sloppy diagnostic overuse of attention-deficit/hyperactivity disorder (ADHD) when "it's just boys being boys," and even of conspiracy in overmedicating children with psychostimulants. In my adult psychiatry practice, I more commonly see the consequences of missed cases of ADHD, rather than overdiagnosis, when, after successful treatment in adulthood, "underachieving" men struggle with a new view of their childhood "failures."

The current case illustrates the need for careful evaluation of inattention. As an adult, Mr. A articulates his anxiety, but as a child, physically active yet silently worried, it would have been easy for an observer to misunderstand the source of his inattention.

The history in his adolescence and early adulthood emphasizes anxiety symptoms. With morbid themes, we must consider the possibility that the anxiety is a component of depression. Pervasive somatic concerns in particular can indicate major depression with psychotic features, a frequently missed diagnosis.

While Mr. A expresses concerns about AIDS and cancer—common themes in delusional depression—his core pathology is excessive worry, the essential feature of generalized anxiety disorder (GAD). Previously, Mr. A met criteria for obsessive-compulsive disorder. His concerns about scrutiny of his behavior also raise suspicion of social anxiety disorder. The complete differential diagnosis would include somatoform disorders, and we should note the comorbid substance abuse history.

So how many diagnoses does Mr. A have?

The disparate symptoms listed in the criteria for GAD cause some to doubt its validity as a true diagnostic entity. The overlap between the criteria for major depression and GAD (*Box 1*) raises other legitimate concerns.

But when we focus on pathologic worry as the defining feature of this disorder and recognize the associated emotional and physical symptoms, I think the diagnosis of GAD captures the essence of Mr. A's presentation. Yes, he met criteria for OCD, and he has features of other disorders, but his current anxiety and physical symptoms are best explained by a unifying diagnosis of GAD.

Box 1

Overlap of DSM-IV criteria for major depression and generalized anxiety disorder

	Major depression	Generalized anxiety disorder
Mood	Depression, irritability	Anxiety, worry, irritability
Psychomotor	Agitation	Restlessness, keyed-up/on-edge feeling
Energy	Fatigue or loss of energy	Easily fatigued
Concentration	Diminished ability	Difficulty
Sleep	Decreased or increased	Decreased or restless/unsatisfying

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Treatment First try at pharmacologic treatment

When Mr. A's worries reached the toxic level of fear of imminent death, he sought a psychiatrist's help. Previous pharmacologic treatment had been limited to brief trials of low dosages of benzodiazepines, typically after emergency room evaluations of some somatic symptom. The benzodiazepines resulted in only minimal improvement and significant daytime sedation. At age 44, at his first appointment with a psychiatrist, Mr. A described not only severe anxiety but also a wide range of physical symptoms. These included tension, dizziness, tingling sensations, migrating pains, disrupted sleep, and low energy.

Mr. A had developed considerable insight about the link between his anxiety and these symptoms, not from psychotherapy but indirectly through extensive medical evaluations. Prior evaluations had included countless emergency room visits, multiple head CT scans and MRIs, and a series of ECGs. None of these led to either a diagnosis or a plan for systematic follow-up until Mr. A independently sought psychiatric treatment.

The psychiatrist prescribed buspirone, titrated up to 10 mg tid, which resulted in minimal improvement of Mr. A's myriad symptoms. But side effects—including generally disrupted sleep and "crazy dreams"—by far offset any gains, and Mr. A in fact developed symptoms diagnostic of major depression. Over the next several weeks, buspirone was discontinued.

In your view, would you now treat Mr. A for depression? If so, with which agent and for how long?

Dr. Carter's observations The salient part of the initial treatment history is the setting. Typical of GAD and panic disorder, much of the early evaluation is done in nonpsychiatric settings. Many patients with anxiety disorders receive no consistent health care. With peak anxiety symptoms manifesting as frightening physical symptoms, such patients present to the emergency room to physicians who are unfamiliar with their longitudinal course. Catastrophic illness is "ruled out," and with the acute anxiety resolved, no fundamental diagnosis is reached.

With Mr. A's medical evaluations, we see a typical example: multiple emergency room visits, repeated brain imaging, and emergency ECGs in a man who exercises vigorously without cardiovascular symptoms. The indirect costs to the patient and to society are staggering, with panic disorder and GAD each ranking above lung problems, hypertension, asthma, and back problems in causing lost productivity at work.[1]

Mr. A is typical of anxiety disorder patients who do not pursue psychiatric treatment initially. Only one-fourth seek treatment,[2] and several variables at the outset of his illness predict an even lower rate for patients such as Mr. A. He is male, had an early onset of illness, and did not have a prominent, comorbid mood disorder. His severe symptoms also predict poor compliance once treatment is initiated.[3]

Understandably, treatment for anxiety disorders often starts with anxiolytics. The common use of benzodiazepines to treat GAD may account for some early studies showing lower sustained remission with GAD compared with other anxiety disorders. Without treating the whole syndrome, sustained response was impossible. In contast, when patients do receive antidepressant medication and stay on it, the literature offers encouragement to those with even severe symptoms: although they do not fare as well as their healthier counterparts early on, patients with severe GAD catch up around the 3-month mark.[4]

Further treatment The move to antidepressants

Mr. A was next started on sertraline, titrated up to 50 mg/d. At this dosage, he complained of significant sexual side effects and early morning awakening that did not respond to trazodone. Sertraline was stopped and the sexual side effects resolved. He began taking nortriptyline titrated up to 75 mg/d without side effects. He reported considerable improvement, with diminished anxiety, resolution of depressed mood, and less dizziness. As Mr. A stated, he was "not such a hypochondriac anymore." Some somatic symptoms per-

sisted, and nortriptyline was increased to 100 mg/d, resulting in further improvement (at a nortriptyline level of 114 ug/L).

After 1 month of being nearly symptom-free, Mr. A experienced a recurrence of his anxiety and an associated increase in depression symptoms, which responded to an increase in nortriptyline to 125 mg/d.

His characteristic health concerns persisted, however. Mr. A was unable to contain his worries about having Huntington's chorea, based on a tremor that he had noted. This particular worry vanished after consultation with a Huntington's disease expert, but from day to day he relied on his wife for constant reassurance about his physical health. Various treatment interventions were discussed, and Mr. A agreed to increase his nortriptyline further. He never did so, however, as the recurrence of his anxiety symptoms proved to be transient.

In fact, his overall improvement was dramatic. He was able to joke about his previous "hypochondriasis," and when thoughts about health concerns entered his mind, he was able to quickly dismiss them and reassure himself. At the outset of treatment, it had not been unusual for Mr. A to make several phone calls *daily* to his psychiatrist seeking reassurance about his general health. During such calls, anything shy of 100% certainty would exacerbate his anxiety. Definitive reassurance would comfort him for anywhere from 1 hour to 3 days. In contrast, on nortriptyline 125 mg/d, Mr. A felt well and would go several months between appointments. His contact with his psychiatrist during those intervals was limited to phone calls to request prescription refills. His phone messages frequently included jokes about whether the psychiatrist was lonely without the frequent phone contact.

How do your patients with complaints of anxiety respond if you suggest treating them with antidepressants? How do you reassure them so they stay the course?

Dr. Carter's observations Educational messages and compliance strategies can have a positive impact.[5] A little time invested in patient education early on can reap big rewards by reducing frantic telephone calls about side effects and the risk of a demoralized patient who discontinues medication prematurely.

For patients who feel every peristaltic wave, knowing that nausea from the initiation of a medication is likely to be gone by the end of the first week of treatment can be pivotal. Such differences are critical in achieving medication trials of adequate duration, which is particularly relevant in GAD.[6] This finding may account for Mr. A's variable early response and more robust subsequent response to nortriptyline.

The importance of educational messages is also relevant to patients' reactions to use of antidepressants to treat their anxiety. This is not a trivial, semantic point. Patients who at first did not even perceive a need for treatment finally recognize that they have *anxiety*, and you are going to prescribe an anti*depressant*? Without a lucid explanation, be prepared for an indignant patient who thinks you are ignoring his or her stated concern. Especially with patients accustomed to the immediate effect of diazepam in acute treatment, the expected time course with antidepressants is a critical lesson.

Regarding specific medications, Mr. A's history again illustrates a typical scenario: benzodiazepines for acute symptoms and buspirone when he eventually presented to a psychiatrist. With typical comorbidity, however, the use of broader-spectrum antidepressants—selective serotonin reuptake inhibitors or serotonin/norepinephrine reuptake inhibitors—represents a more logical first-line choice. Head-to-head trials between venlafaxine XR and buspirone further support this position.[7] With the emergence of sexual side effects with sertraline in this particular case, the switch to a different category of antidepressant is sensible.

I support the use in GAD of antidepressant dosages comparable to those used to treat major depression. I can recall discussions about how anxiety disorder patients cannot tolerate full doses of antidepressants and do not need them anyway, but dosage response studies and clinical experience would argue otherwise. Compliance is a crucial factor with anxiety patients, and nothing fosters compliance like robust clinical response. In treatment of GAD, the data are clear: Use antidepressants at full dosages.

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Complications hypochondriacs get ill, too

Mr. A remained well for 8 months, but then became more concerned about an increase in his resting heart rate to 90 bpm, some heartburn, and a slight decrease in his libido.

At Mr. A's request, liver function tests (LFTs) and an ECG were obtained. The latter was normal, but his LFT scores remained elevated (ALT=121, AST=73) without significant change from premedication results (130, 64, respectively).

Three months later, Mr. A continued to report that he was feeling well, but he now noted distress related to long-term memory deficits that had emerged, in retrospect, relatively early in this nortriptyline trial. His dosage was decreased to 100 mg/d.

At a routine physical examination the next month, Mr. A's internist noted the persistence of elevated LFT scores. The internist had been advised of Mr. A's anxiety-ridden response to any discussion of possible medical illness and agreed to simply recommend that Mr. A discontinue his vitamin A and D supplements with periodic administration of LFTs.

A year later, however, with advancing knowledge about chronic hepatitis, the internist found that Mr. A did indeed have hepatitis C. Mr. A handled this news relatively well initially, but 4 months later his defenses began to break down. His previously lighthearted humor assumed more morbid tones, as he attempted to joke about how he would probably die from liver cancer while he worried about a hangnail. He became dependent on his wife's reassurance again and required her presence during appointments so that she could retain information from those meetings and later use it to reassure him.

The role of his moderate alcohol intake came under more scrutiny, and his psychiatrist advised Mr. A to stop drinking altogether. Transient episodes of severe anxiety were treated with low doses of lorazepam over several weeks. Mr. A began to obsess about the timing of any further work-up regarding his hepatitis C, including the question of a liver biopsy. He wanted to make sure that he did not get any LFTs prior to travel, knowing that he would obsess about the results and ruin the vacation for his wife and himself.

Several months later, after more than 3 years on nortriptyline, it became clear that Mr. A's anxiety about his hepatitis—combined with his ongoing concern about memory side effects—indicated a need to change his medication. A taper of nortriptyline resulted in significantly increased anxiety symptoms, but also in an obvious improvement in his memory.

In your view, what would be your next choice of therapy? Another antidepressant? Back to an anxiolytic? Why?

Dr. Carter's observations The general goal is to maintain long-term compliance with treatment of a chronic condition. Therefore, judicious use of benzodiazepines as adjunctive treatment might play a crucial role during flare-ups of the illness, as when Mr. A learns that he actually has a serious medical condition other than his anxiety disorder. We have already established that anxiolytics are not a sensible choice as the foundation of treatment, but they can help patients who experience temporary increases in anxiety with initiation of antidepressant treatment.

We have already reviewed the critical nature of education in treatment, as anxiety limits one's ability to process new information. Mr. A's idea of bringing his wife to appointments is a simple and elegant means of his later testing any possible distortions of the conversation. I have patients who audiotape sessions for their subsequent use, and anxious patients frequently attribute significant value to the chance to review certain points "on their own turf" and when their anxiety level is optimally reduced for learning.

In the case of Mr. A, there was a sound working relationship between the internist and the psychiatrist, which is an asset in managing somatic presentations of anxiety disorders, particularly with the risk of depression and even suicide associated with potential interferon treatment of hepatitis.

Final chapter Confronting anxiety, side effects

Fluoxetine was the next form of treatment, subsequently titrated up to 60 mg/d. Mr. A's worries about the state of his liver improved, but he was still troubled by infrequent, brief episodes when his anxiety would soar. The overlap between nonspecific symptoms of progressive liver disease—nausea, fatigue, and abdominal pains—and Mr. A's baseline anxiety symptoms presented new fodder for his anxiety.

His response to fluoxetine illustrated a clear dose-response relationship: His anxiety improved after each dosage increase, and symptoms escalated whenever the dosage was decreased to address a given side effect. Mr. A reported tolerable sexual side effects but ultimately nightmares were too distressing, limiting the quality of his nighttime sleep and resulting in daytime fatigue.

To address this sleep disruption and sexual side effects, fluoxetine was discontinued and Mr. A began taking nefazodone. He took up to 375 mg/d for approximately 20 months with moderate benefit, offset only somewhat by a recurrence of vivid dreams. Then case reports appeared possibly linking liver failure to nefazodone. Mr. A agreed to stop this agent and to evaluate gabapentin as an anxiolytic.

With limited dosages of gabapentin, up to a total of 1,200 mg/d, Mr. A noted significantly improved anxiety symptoms overall, but nightmares and other vivid dreams still interfered with his recovery.

No clear correlation between medication or anxiety level and severity of sleep disturbance emerged. The nature of Mr. A's work rendered the "sleep hygiene" intervention of a regular sleep cycle impossible, and he understandably did not consider a career shift feasible. A sleep disorders consultation to address this one remaining symptom is under way.

Overall, Mr. A is delighted with his progress. He is now able to participate in informed decision making about treatment of his hepatitis, rather than merely obsess about obtaining LFTs.

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Related resources

- Anxiety Disorders Association of America. www.adaa.org. Information for psychiatrists, researchers, residents, patients, caregivers, and the media
- About.com: Generalized Anxiety Disorder: A Real Illness. http://www.MentalHealth.About.com/library/mh/anx/blgadri1.htm
- National Institute of Mental Health: Anxiety Disorders http://www.nimh.nih.gov/anxiety/anxietymenu.cfm

DRUG BRAND NAMES

Buspirone • Buspar
Diazepam • Valium
Fluoxetine • Prozac
Gabapentin • Neurontin
Lorazepam • Ativan
Nefazodone • Serzone
Nortriptyline • Pamelor
Sertraline • Zoloft
Trazodone • Desyrel
Venlafaxine • Effexor

DISCLOSURE

The author reports that he received research support from Eli Lilly and Co. and Pfizer Inc., and serves as a consultant for Eli Lilly and Co. and Ortho-McNeil Pharmaceutical.

Bottom Line

Early detection of GAD would greatly benefit the patient—and the health care system as a whole. First-line pharmacologic treatment involves use of SSRIs or SNRIs at dosages comparable to those used to treat major depression. For severe anxiety, continue the medication for at least 3 months. Early education is critical to fostering compliance.