Generalized Anxiety Disorder: Between Now and DSM-V

Christer Allgulander, MD, PhD

KEYWORDS

- Anxiety disorders
- Classification • Anti-anxiety agents
- Antidepressive agents • Pharmacology
- Generalized anxiety disorder • GAD • DSM-V

Generalized anxiety disorder (GAD) differs from other anxiety disorders and from depression in terms of the pervasive cognitive dysfunction and associated prospective threat scenarios. It is accompanied by subjective tension, pain, sleep disturbance, fatiguability, and irritability, conducive to impaired performance in work, leisure, and family life. It is the most common anxiety disorder in medical treatment settings, and it increases the disease burden in cardiovascular and cerebrovascular disease, pulmonary disease, and diabetes mellitus. GAD is amenable to several pharmacotherapies and to cognitive behavioral therapy (see the article by Hoyer and Gloster in this issue).

This article presents the current evidence base for pharmacotherapy of GAD and an update on the phenomenology of GAD and its association with other psychiatric and somatic conditions. It discusses nosological issues and suggests ways to improve recognition, treatment, and care for patients who have GAD.

Patients who have GAD are excessively concerned with the safety and comfort of the immediate family and oneself.[1] Here are some examples of this kind of dysfunctional thinking:

> *"What if Eva had breast cancer—would we have to move out of the house? Will junior be able to complete his studies, considering the problems his girlfriend are causing him? Why is Gertrude late from kindergarten; has there been an accident? I have double-checked the report, but I had still better go to the office on Sunday to make sure, considering the consequences if I have overlooked something. I cannot stop worrying all the time about the bills at the end of the month although I have always been able to pay them on time."*

Department of Clinical Neuroscience, Karolinska Institutet, Section of Psychiatry at Karolinska University Hospital, SE 141 86 Huddinge, Sweden
E-mail address: christer.allgulander@ki.se

Psychiatr Clin N Am 32 (2009) 611–628
doi:10.1016/j.psc.2009.05.006 **psych.theclinics.com**
0193-953X/09/$ – see front matter

Although these thoughts (talking to oneself) seem trivial at first glance, they preoccupy the subject's cognition, draw attention and energy, and cannot be put aside. They are future oriented and differ from depressive ruminations that deal with past failures and are associated with guilt feelings. In obsessive-compulsive disorder obsessions typically concern orderliness, contamination, and moral issues. Patients who have GAD often say that they have always worried excessively about minor matters to a degree that eventually impairs their social functioning. The worry serves to preempt episodes of exacerbated fear in an imaginary world with negative emotional affect. The somatic manifestations of GAD, particularly tension, evolve and finally lead to social consequences such as impaired work performance, reduced leisure activities, and a tense and irritable family atmosphere.

THE EVIDENCE FOR SPECIFIC FORMS OF PHARMACOTHERAPY FOR GENERALIZED ANXIETY DISORDER

The current regulatory climate determines how pharmacotherapies for GAD are made available to the public and encourages new measures, reproducibility of results, transparency, and accountability. The value of an anxiolytic for GAD now is measured in at least four domains: independent randomized, controlled trials in support of anxiolytic efficacy versus placebo and active compounds (always including the Hamilton Rating Scale for Anxiety, HAMA), an estimate of the risk of relapse into GAD upon treatment cessation after responding, self-ratings on restoration of social functioning, and clinical safety for up to 6 months of therapy. The recent regulatory request for noninferiority analyses in GAD studies stems from the increasing availability of medications for some disorders (eg, antibiotics, antihypertensives, and antidepressants/anxiolytics); noninferiority to a comparator drug should be demonstrated, based on predefined sets of statistical and clinical criteria.[2] In addition to satisfying these regulatory requirements in phase II to phase III studies, a wealth of data derived from secondary analyses (''data-mining'') provide a basis for generating and testing new hypotheses, such as gender differences in symptom pattern and treatment response in cases of primary GAD, pharmacogenetic and clinical predictors of response and remission, and pharmacodynamic correlates to adverse drug reactions. Efficiency studies demonstrate the direct and off-set savings for the individual and for society that are realized by identifying and treating patients who have GAD.

Recent study programs of GAD anxiolytics have not been burdened with nonconclusive studies, contrary to the situation 10 years ago, when every other GAD study failed to distinguish active drug from placebo.[3] This improvement is a result of the improved training of clinicians in trials, the inclusion of patients with more psychopathology, and the use of sensitive objective and subjective rating instruments.

Although clomipramine, desipramine, and alprazolam were approved by regulatory bodies in the early 1980s for treating patients who have panic disorder, the first approval of a medication for GAD was given much later, with venlafaxine, in 1999. There was a need for new maintenance medications because benzodiazepine anxiolytic treatment had become restricted to short-term use.

Buspirone was approved for symptoms of GAD by the Food and Drug Administration in 1985, but most of the studies were performed in the 1970s in patients diagnosed with psychoneurosis, which, according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders,* edition 2 (DSM-II), could include substantial depressive symptoms. They then were re-diagnosed retrospectively with the GAD criteria specified in the third edition of the DSM (DSM-III).