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REVIEW ARTICLE

Generalized Anxiety Disorder: A Review of Recent Findings

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Generalized anxiety disorder (GAD) is characterized by a pervasive cognitive dysfunction with a focus on threats and risks toward the individual or his/her immediate family. It goes with tension, worry, muscle pain, disturbed sleep, and irritability that all together impair work capacity, relations, and leisure activities. By its chronic course, GAD increases direct and indirect costs for the individual, the family, the health care services, and at work or in education. Among patients with cardiovascular or cerebrovascular disease, pulmonary disease, diabetes, and neurological diseases, GAD is a risk factor for somatic complications and for lowered adherence to somatic treatments. GAD can be treated with cognitive behavioral therapy, and/or with medications.

1. Introduction

This paper is intended to update the academic or practising psychiatrist about the current state of knowledge of Generalized Anxiety Disorder, emphasizing that its chronicity is a factor to consider in somatic disciplines as well.

2. Clinical characteristics

Generalized anxiety disorder (GAD) is a psychiatric diagnosis in the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* and in the *Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition.* Individuals with GAD are characterized by a pervasive and uncontrollable state of worry (apprehensive expectation). Primarily, they seek treatment by practitioners not for worry but for disruption of sleep, muscle tension, dyspepsia, restlessness, fatigability, and irritability. This primary cognitive dysfunction, paired with secondary somatic anxiety manifestations, impair the capacity for work, for relations, and for leisure activities. GAD also increases the risk for subsequent depressive episodes, self-medicating with alcohol, and complications in concurrent somatic diseases.

In their reality management, GAD patients display a basically distorted view on risks and threats, particularly those that concern the health, security, and welfare of the individual and his/her immediate family members. This distortion of imagined future events is different from the cognitive dysfunction in depressed patients, who mainly recollect past failures and mistakes that cause ruminations, guilt feelings, and feelings of worthlessness. The cognitive distortion seen in GAD also differs from that in obsessive-compulsive disorder that chiefly deals with symmetry, contamination, and ambivalence in moral issues.

GAD patients worry prospectively about hazards: *what if* our business goes bankrupt, *what if* our daughter is run over on her way from daycare, *what if* we get robbed on our summer trip or we have an accident far away from home. Work mates and family members testify that a person with GAD exaggerates thematically concerns over potential events in ordinary life, that the person is a "worrywart."

Culturally, daily worries are dealt with by simple methods such as manipulating rosaries in Islamic and Jewish tradition, or polished stones, and in Guatemala by talking about worries with little dolls that are put under the pillow at night.

Several thought leaders have made substantial contributions to our understanding of GAD, to mention a few: Gavin Andrews, Jules Angst, David Baldwin, Borwin Bandelow, Johan den Boer, Tom Borkovec, Jonathan Davidson, Jack Gorman, Marty Keller, Kenneth Kendler, Donald Klein, David Nutt, Stefano Pallanti, Mark Pollack, Karl Rickels, David Sheehan, Dan Stein, and Hans-Ulrich Wittchen.

Imaging studies of the amygdala and associated neuronal circuits show an enhanced base activity, as well as an increased reactivity to stimuli, indicating that there are deficits in emotional processing that the individual is not aware of.[1–3] Medications have been shown to normalize this state of alertness parallel to a reduction of reported anxiety symptoms.[1] Sympathetic activation that is normally reduced at night remained high in a laboratory study of GAD patients.[4] Inhaling carbon dioxide resulted in anxiety symptoms and vegetative activation in GAD patients.[5,6]

Several psychological theories have been proposed to explain the cause of worry and how worry is maintained. Borkovec and Roemer[7] theorize that the function of worry is to avoid, causing an

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ineffective problem solving. Worry about imagined events suppresses negative thoughts and images and strengthens avoidance behavior. Another theory stresses the importance of intolerance of uncertainty.[8] Worry arises when not trusting information. A third theory concerns so-called meta-cognition, by which the patient believes in worry preventing catastrophes, with meta-worry (worry about worrying) as a consequence.[9] Since worry becomes such an important strategy, it gets a life of its own. Finally, there is extensive research into how GAD patients manage information by cognitive schemata and selective bias toward threats.[10] Support for worry being a trait rather than state was found in a recent study of Dutch adolescents who were followed over a period of 5 years.[11]

3. Prevalence of GAD in population samples and in primary care

European and U.S. prevalence studies show similar rates of GAD in the adult population. For example, a representative sample of 10,000 twins in Sweden aged 55–74 years was interviewed about GAD symptomatology.[12] The lifetime risk of GAD was estimated at 3.95% in women and 1.74% in men. The genetic contribution was 27% and individual environmental factors 72%. Thus, only 1% was accounted for by shared environment, such as parenting.

A British population study found that 3% of those interviewed had GAD, and only 8% of those diagnosed with GAD were in treatment with medications or psychotherapy.[13] A population-based survey of GAD in Hong Kong found a 3.4–4.0% 12-month prevalence.[14]

Turning to GAD in health care settings, the chances of identifying the disorder are influenced by comorbidity. Secondary depressions are common in GAD, as shown in prospective and longitudinal studies.[15] This is usually the time when a GAD patient first seeks help, after several years of trying to cope with worry. General practitioners more easily recognize GAD patients who appear with secondary depression and are more likely to institute treatment.[16]

On a typical working day in 2001, 648 general practitioners in Sweden and their 8879 patients participated in a comprehensive survey to identify cases of GAD in primary care.[17] The age-standardized rate of GAD was 4.1–6.0% among men and 3.7–7.1% among women.

Ethnic aspects influence the symptomatology of anxiety disorders, with a shift toward somatizing in Asians, called distress syndromes.[18,19] GAD, panic disorder, and posttraumatic stress disorder may have other names in Asian cultures stemming from traditional medicine in China, Cambodia, Vietnam, and Thailand—for example, *shenjing shuairuo*, wind overload, weak heart and weak kidney, and neck soreness. *Hwa byung* is marked by catastrophic cognition about negative emotions in Korea. Neurasthenia is another term used in Japan and China that probably overlaps with GAD. Illness attribution and illness presentations need to be considered in treating patients in their ethnic environment or in migration to western society. The pharmacodynamics and pharmacokinetics of medications for GAD, usually assessed in western populations, may also be influenced by pharmacogenetic factors.[20]

4. Somatic comorbidity

Morbid anxiety influences the course of several somatic diseases, particularly neurological, cardiovascular, pulmonary, dermatological, and endocrine diseases.[21] Anxiety can arise as a consequence of being given a diagnosis of a serious somatic disease. It can also be a direct consequence of a neurological trauma such as a stroke or a traumatic brain injury, and it may be a primary concurrent anxiety disorder. A potential issue in assessing such patients is that anxious patients with somatic diseases perhaps may aggravate their problems to a degree that does not match with objective criteria of severity.

Considerable interest is now devoted to nonmotor symptoms in Parkinson's disease, including anxiety, that may precede the onset of motor symptoms by many years.[22] Anxiety can be more burdensome than seizures in patients with epilepsy.[23]

Anxiety is an independent risk factor for cardiac events, as several studies have shown. For example, significantly more cardiac events occurred within an 8-year period in patients with coronary heart disease, in those who were anxious at baseline compared to those were not.[24] The National Health Research Institute of Taiwan runs the Taiwanese National Health Insurance Research Database with *ICD-9* diagnoses, prescribed medications, age, and gender. A study of 913,570 cases of anxiety disorder treated with psychoactive medications during a 4-year period compared the rate of ischemic heart disease and hypertension to residents without such treatment.[25] The relative risk of having treatment for ischemic heart disease was a 10-fold increase in treated anxiety patients below age 20 and a 5-fold increase in those treated for hypertension. This finding of adolescent cardiac risk factors needs to be further investigated. These risks decreased substantially with age, as cardiovascular disease becomes more common in the matched population.

Another Taiwanese national study looked at whether panic disorder first diagnosed in 2004 increased the risk of a first myocardial infarction during a 12-month period.[26] The 9641 probands were compared to 28,923 matched healthy controls. Probands were more likely at baseline to have hypertension, hyperlipidemia, and coronary heart disease, and less likely to have diabetes and renal disease. A subsequent first myocardial infarction occurred in 5% of the probands and 3% of the controls, yielding a hazard ratio of 1.8.

The risk of contracting type 2 diabetes was increased by baseline anxiety or depression, even when adjusting for other well-known diabetic risk factors, according to a well-designed population-based prospective study in Norway.[27]

Pain is an underestimated phenomenon in psychiatric patients in general, and in anxiety disorders including PTSD, although pain and anxiety are closely related entities.[28] Chronic neuropathic pain, affecting a large portion of elderly people, is strongly associated with depression and anxiety. Chronic pain often preceded a diagnosis of GAD in a German population-based study.[29] Painful physical symptoms frequently accompanied GAD in primary care according to a recent study in Spain.[30] It is interesting that pregabalin is approved by regulatory authorities in Europe for both neuropathic pain and GAD, while in the United States it is approved for fibromyalgia, another pain disorder associated with GAD.[31] Duloxetine, approved for GAD in Europe and in the United States, is also approved for fibromyalgia in the United States.

How does a practitioner best approach a patient with GAD? One may apply screening instruments such as GAD-7, recommended by the *Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition* committee for GAD (www.dsm5.org), and confirm the diagnosis with the aid of the MINI Neuropsychiatric Interview (www.medical-outcomes.com). With many confounders that may obscure a diagnosis of GAD, a basic medical examination and history should include tests for substance use, thyroid disease, and investigation of prominent gastrointestinal symptoms as well as suspicion of an incipient neurological disease. Beta-stimulant medications, corticosteroids, and several other medications may cause anxiety symptoms as well. Pain should be assessed using a visual analogue scale, and scores can be monitored during treatment intervention in conjunction with objective and subjective measures of anxiety.

5. Insomnia in GAD

Sleep is of fundamental restorative importance to maintain health in most species, and disrupted sleep is one of the early indicators of relapse or exacerbation of affective and psychotic disorders. Contemporary researchers theorize that the modern 24/7 society and its basic lack of efficient sleep contributes not only to the burnout syndrome, but to many other stress-induced states. At least every other GAD patient sleeps poorly, and has reduced sleep quality, reduced total sleep time, and less time in sleep stages 3 and 4.[32] A Swedish study of GAD patients in specialized outpatient care found that a high proportion were on hypnotic medications in addition to maintenance treatments on serotonin modulators, particularly so in the elderly.[33] The prognosis in anxiety disorders, particularly PTSD, is influenced by sleep problems.[34] Interestingly, one study noted that if poor sleep was addressed by hypnotic drug therapy in addition to anxiolytic therapy, the response of GAD patients improved.[35]

6. Cost of illness studies

Since GAD is a chronic disorder and the most frequent anxiety disorder in health care, it is important to realize its costs for society and for the individual, even more so in view of the demographic shift toward the elderly in many societies. According to a European study of disorders of the brain, GAD incurs substantial direct health care costs, as well as indirect costs for work absenteeism and burden to others.[36] A recent review on the burden of GAD in society confirms these data.[37] A national health registry in Sweden was performed for all GAD patients treated in specialized psychiatric units during the calendar year 2006.[33] They incurred a cost per patient of SEK 5520 for medications, SEK 7698 for outpatient visits, and SEK 92,152 for those requiring inpatient treatment.

7. Evidence-based GAD treatments

The most recent international guideline for drug treatment of GAD was published in October 2008 by a task force appointed by the World Federation of Biological Societies of Psychiatry WFSBP.[38] The first-line treatment for GAD was an serotonin and noradrenaline reuptake inhibitor (SNRI) or an serotonin specific reuptake inhibitor (SSRI) medication, or pregabalin. Consideration was not given to cost of treatment as this varies between countries. The medications approved by European regulatory authorities for GAD, based on extensive phase III studies, are escitalopram, venlafaxine, duloxetine, paroxetine, and pregabalin. In 2010, the Swedish national board of health and welfare issued similar guidelines, adding benzodiazepines as a third-line treatment option. Cognitive Behavioural Therapy (CBT) is also a recommended treatment for GAD, although the studies are generally small and of varying quality.[39–41] Fifty percent of those who completed treatment and 40% of those who started treatment in controlled studies showed an improved functioning. The CBT technique involves psychoeducation, acceptance, time to control and to master worry, and advice how to avoid relapse, sometimes Internet-mediated. With regard to combining CBT with pharmacotherapy, a pragmatic study found that few patients accepted the offer of add-on CBT, and that no added benefit could be demonstrated.[42]

The British Association for Psychopharmacology is due to release its updated guideline for anxiety disorders treatment in 2012 (www.bap.org.uk).

With the waxing and waning course of GAD, the expert opinion is that a patient should continue drug treatment for at least a year if there is an initial response in order to optimize the chance for remission. Adverse drug effects may call for a change of dosing, or a switch to other pharmacodynamic principles. Generally, the risks of not treating anxiety, particularly risk of cardiovascular consequences, diabetes II, secondary depressive episodes, and self-medication with alcohol, outweigh the risks of serious drug adverse effects. This general attitude also pertains to pregnancy, as there are also consequences for the fetus of untreated anxiety.[43] Conservatively, fluoxetine and sertraline are preferred drugs in pregnancy as these medications have been used extensively.

GAD patients who do not respond to the first-line treatment can be offered benzodiazepines or a third-generation antipsychotic, among which quetiapine has shown efficacy in several short-term studies.[44] The clinician must rely on clinical experience as second- and third-line treatments, including adjunct combinations, have not been sufficiently evaluated in controlled trials.[45] European psychiatrists, according to a recent survey, find that most of their referred GAD patients have already been prescribed benzodiazepines by other physicians, and that the psychiatrists' first-line treatments are an SSRI, an SNRI, or pregabalin.[46] One may consider the reasons for failing to respond, such as substance use, personality disorder, and not adhering to dosing regimens.

8. Conclusion

Taken together, GAD is a common and costly anxiety disorder with chronicity over the years, increasing the risk for somatic and psychiatric comorbidity, and cause for maintenance treatment in many instances. The demographic changes in many societies will increase the number of elderly in need of treatment.[47] Since elderly patients are excluded from most phase III trials, we have little knowledge today how to manage them, especially considering the amount of somatic comorbidity, and potential for interaction with other medications.

Anxiety is currently seen as a developmental disorder, a result of gene by environment interactions that can induce structural and functional changes in an amygdala-prefrontal circuitry. Anxiety disorders are genetically complex, and the phenotypes may be the expression of gene by gene as well as gene by environment interactions.[48] Candidate gene findings have not been specific and replicable. Apparently, genome-wide scanning of tens of thousands of probands and controls are necessary to advance the field.

Conflict of interest

The author is an advisor for Pfizer-Sweden as well as a speaker for Pfizer-Europe and Servier. He reports that he has not received any funding in writing this review. Winston W. Shen has reviewed the contents of this article, and found no evidence of conflict of interest.

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