Pakistan Journal of Neurological Sciences (PJNS)

Volume 8 | Issue 1 Article 6

1-2013

Generalized anxiety disorder: can we rest now?

Aamir Abbas
Aga Khan University Hospital Karachi,pakistan

Haider A. Naqvi
Aga Khan University, Karachi

GENERALIZED ANXIETY DISORDER: CAN WE REST NOW?

Dr. Aamir Abbas1, Dr. Haider A. Naqvi[2]
1 Department of Community Health Sciences, The Aga Khan University, P.O. Box 3500, Stadium Road, Karachi74800, Pakistan
2 Department of Psychiatry, The Aga KhanUniversity, P.O. Box 3500, Stadium Road, Karachi74800, Pakistan

Correspondence to: Dr. Haider A. Naqvi, Department of Psychiatry, The Aga Khan University, P.O. Box 3500, Stadium Road, Karachi74800, Pakistan: haider.naqvi@aku.edu

ABSTRACT

Generalized anxiety disorder is a complex psychiatric syndrome. Current understanding on the epidemiological risk factors, genetic vulnerability and neurobiology of the GAD is beginning to unfold the complexities behind this disorder. This narrative review has attempted to put together the recent advances in the area of GAD research with intent to identify the gaps requiring further research.

INTRODUCTION

Anxiety is a great modern day plague. It has reached a pandemic proportion. The concept of Anxiety disorders, as explained in the psychiatry nomenclature, has various descriptions. The focus of classification is on physical manifestation of psychological symptoms. This has steamed from the behavioral model of psychology. One of the key proponents of this conceptualization was Sir William James (1842-1910), famous American psychologist and philosopher, who described the relationship between body and mind. The classification system has undergone periodic revision over the course of years whence the description of symptoms and their numbers, required to make a diagnosis, has changed. The neurobiological understanding of the disorder has also changed over the course of time. This review will focus on the epidemiological, genetic and radiological underpinning of the GAD.

Generalized anxiety disorder (GAD) is characterized by persistent, pervasive and uncontrollable state of worry which is disproportionate to its source and lasts for at least six months.1(Table 1)

Prevalence of GAD:

The prevalence of GAD is varies from different studies in different populations. The use of diagnostic conventions, whether the ICD - 10 or DSM IV diagnostic criteria, also contributes to the variability of estimates.2According to a recent NHANES data base the prevalence of GAD in the United States(US) children is 0.7%.3 According to National Co-morbidityAdolescent Supplement Study the life time prevalence of various anxiety disorders in US adolescent population is 31.9%. The life time prevalence of GAD is reported to be [2].02%. 4The prevalence of GAD increases consistently with age. It is reported to be 1% in the age group of 13 to 14 years of age while[3] % in the age group of 17 to 18 years.[4]The prevalence of GAD in the US population have been reported to range between 2 to 9% across all age groups.[5] The prevalence of GAD is more in females (3%) as compare to males (1.5%).[4]The twelve month prevalence of GAD in geriatric population of US has been reported to be 2.8%.

The twelve month prevalence of GAD in the European population has been reported to be 2%.[6]The one month prevalence of GAD is 4.1% in Sweden.[7] Most of the GAD patients in European Union (EU) present to the primary health centers.[6] Many of these cases remain unrecognized. A study from EU reported that almost half of the patients with GAD were left un-diagnosed when consulting their general practitioners. [8]Similarly, in Asian countries, like China the one month prevalence of GAD ranges from 2% to 2.9%.[9] The life time prevalence of GAD in Hong Kong range from 5% to 10%.[10] A study done on adolescents in India showed the prevalence of GAD to be 19%.[11]The general population based survey from Iran reports the prevalence of GAD to be 0.73%.[12] In Pakistan the prevalence of anxiety disorders in a semi urban population was found to be 30%. [13]

Risk factors of GAD:

Various factors which affect the pattern of 'repetitive thoughts' of 'worrying' nature has important bearing on conversion of physiological anxiety to pathological anxiety and hence GAD.[14]Age is an important epidemiological

variable and risk factor for some disorders; one study showed a declining patterns of anxiety with increasing age .[15] Prevalence of GAD was found to be highest in the age group of 15 to 45 years.16 GAD is also reported to be higher among women as compare to men.[16] Although marriage is a protective factor against mental illnesses, a cross section, community based study from Pakistan found a higher prevalence of psychiatric morbidity (including GAD) in a sub-sample of married females.[17, 18]

Alcohol abuse and dependence is also known to increases the incidence of GAD.[19] Benzodiazepines are normally used to treat GAD.[20]However, taking benzodiazepines without prescription and easy availability (over the counter sales) results in addiction.[20] Individuals (develop dependence and) experience withdrawal anxiety if they do not get benzodiazepines.[20] Therefore these drugs paradoxically become the cause of GAD.[20] Low education is a known risk factor for many mental disorders.[21] Psychiatric co-morbidities like depression, borderline personality disorder and schizotypal personality disorder have been reported to be associated with GAD.[19, 21] Mood disorders, like major depressive disorder (MDD) are co-morbid with GAD. This is explained by a shared etiology for both the disorders.[21] Romantic relationships have paradoxical association with anxiety.[22] It was found that dating decreases anxiety but disturbed relationship with the partner increases anxiety and may predispose a person to GAD.[22] Presence of regular work opportunity has been reported to be protective against GAD.[23] Socio-economic status has an effect on GAD. However the nature of this effect is inconclusive from the previous studies in Pakistan.[23]Pathological Internet usage also predisposes a person to GAD.[24] Loss of spouse predisposes a person to GAD.[17]GAD, like most mental disorders, is associated with significant morbidity. One way to quantify the burden of disease is to quantify the cost of care for individuals and the society.

Cost of GAD Care:

GAD puts a lot of cost on the society as direct health care cost as well as cost due to productivity losses.[25] The direct health care cost is large because studies have shown that in developing countries patients with different types of anxiety are high utilizes of the health systems for curing their mental illness.[26] The cost of GAD reported varies depending on a number of factors important ones being the country in which the study is being done and the methodology of the study. The methodology adopted for costing of GAD varies significantly between different studies. Some of the studies tried to find out the cost of prevalence i.e. finding one year cost of GAD that includes direct and indirect cost. Another type of cost estimation was from cohort studies which found out cost from incident cases. Another important variability in the cost of GAD coming out from different studies is because all studies used direct cost but very few studies used direct as well as indirect cost of GAD.

In one study the total one year cost of different anxiety disorders in US was reported to be 46,551 million USDs out of which 10,748 million USDs was the direct cost while 35,436 USDs was the indirect cost.[26] The prevalence of GAD among these patients was found to be 40%.[26] With multiple regression analysis, looking to estimate the individual cost of GAD, figure came to be 42,300 billion USDs which was around 1,542$ per patient.[27] This cost includes direct as well as indirect cost adjusted for many other independent variables. GAD is a condition which is frequently found co-morbid with other disorders. The co morbidity increases the cost of both the conditions i.e. GAD as well as the co-morbidity as has been demonstrated in migraine.[28]

New Genetic findings related to GAD:

Genetic makeup of a person has been reported to be responsible for giving different responses to the drug treatment. This has been demonstrated in a recent study in which the response to venlafaxine was lower in the group having a La/La+G/G or La/La+G/A genotype.[29] An important gene which has been recently studied through knockout studies of mice is GABA and its role of y2-/- versus y2+/- genes.[30] It was demonstrated that the vulnerability of mice to anxiety changed after manipulating these genes through knockout techniques.[30] What is the role of these genes in human beings and their anxiety status needs to be evaluated.

In a pilot study involving different metabolites which include L-amygdala Cr, L Amygdala ml (L+R), R-hippocampus Glx, OFC Cr and OFC NAA have been reported to affect the GAD status of a person.[31]Authors concluded that all genes directly or indirectly effecting these metabolites which have an impact on different anxiety disorders including GAD.[31]

The findings of this study is needs to be confirmed through more robustly designed and adequately powered studies.

The effect of genes that include 5-HTTLPR,

COMTval158met, and BDNFval66met on the treatment outcome of social anxiety was studied through a randomized control trial where Internet-based cognitive behavior therapy (ICBT) was compared with cognitive behavioral group therapy for (CBGT).[32] No significant effect was found of these genes on the treatment outcomes. The effect of antidepressants on the treat GAD is hypothesized to be effected by variant rs4680 of COMT gene. In one study the effect of this particular variant of COMT gene on the anxiety status of a people in the European American sub sample was positively associated. These finding can be confirmed through further studies.[33]

If the parents are suffering from a particular anxiety disorder, the risk of children for suffering from different anxiety disorders increases. The precise cause of excessive vulnerability, whether genetic or environmental, needs to be separated out in further research.[34]A Meta-analysis done to find out the effect of genetic versus a (shared) environment in separation anxiety disorder concluded both genetic and environmental effect are present.[35] Since there are important conceptual differences between GAD and separation anxiety disorders, we cannot directly generalize the findings of this meta-analysis to GAD patients.

Neuroimaging and GAD:

Different brain areas are involved in the neurobiology of GAD. Bed of nucleus striaterminalis, the insula, anterior orbitofrontal cortex, hippocampus, anterior cingulated cortex and amygdala are important regions out of many others.[36, 37] In one study the volumes of amydala was reported to have increased in children and adolescents living with a case of GAD.[38] Stressful response in GAD results in decreased activity in amygdale and increased activity in bed of nucleus stria terminalis.[36] These decreased and increased responses were picked through fMRI.[36] This study generated the hypothesis of decreased activity in amygdale and increased activity in bed nucleus of striaterminalis.[36]

It was reported that young patients with GAD had an increase in the volume of gray matter in right precuneus and right precentralgyrus while the gray matter in the posterior cingulate and left orbital gyrus is decreased.[39] Further, in the same study it was reported that in the GAD patients, the white matter is decreased in superior frontal and left medial gyrus whereas it is increased in left inferior temporal gyrus.[39] These comparisons were elicited using voxel-based morphometry.[39] In a sample of sixteen women it was found that the volume of dorsomedial prefrontal cortex increased, which can be detected through MRI.[40] Another important parameter raised in GAD is N-acetylaspartate/creatine ratios in dorsolateral prefrontal cortex and it is assessed using proton magnetic resonance spectroscopy.[41] This ratio was 16.5% higher in one study with a total sample size of 30 individuals. [41] GAD patients were found to have increased apparent diffusion coefficient in right parietal cortex and right splenium using a diffusion weighted magnetic resonance imaging.[42] More focused work where the functional connection of different nuclei of amygdale in GAD patients' needs to be was evaluated.[43] GAD patients were found to have problems in connection of different nuclei of amygdale.[43] Some studies have evaluated this using resting stage functional magnetic resonance imaging. Further it was found that as the severity of GAD increases, the problem with functional connection among the different nuclei of amygdale also increased.[43]Centro medial and basolateral amygdala was identified as the most problem area in GAD patients.[43]

Treatment of GAD:

The evidence based treatment of GAD can be dichotomized in to psychological and psychopharmacological intervention. In following sections we will present a brief overview of the treatment. Those interested in knowing the further details are advises to consult the cited reference material.

Psychological treatments While the general relaxation technique, breathing exercises and guided imagery are indicated in most cases of GAD, there are various forms of psychological treatment which are specific for therapies include client centered, supportive-expressive and rational emotive therapies. [44]

It is recommended that psychological intervention be started first before going for pharmacotherapy. However, in a developing country like Pakistan, where on one hand there is a dearth of trained clinical psychologists and the prevalence of GAD is greater than many other countries bringing the recommendation of trying the psychotherapy before pharmacotherapy becomes a real challenge. Further, the problem is complicated as very few of the psychotherapies are culturally adapted for the indigenous population. Therefore completing the bio-psychosocial model for the treatment of GAD patients becomes a real challenge for the practicing physicians.

Table **1**

ICD 10 Criteria for Generalized anxiety disorder (WHO ICD 10 criteria for research)

a. A period of at least six months with prominent tension, worry and feelings of apprehension, about every-day events and problems.

b. At least four symptoms out of the following list of items must be present, of which at least one from items(1) to (4).

Autonomic arousal symptoms

(1) Palpitations or pounding heart, or accelerated heart rate.
(2) Sweating.
(3) Trembling or shaking.
(4) Dry mouth (not due to medication or dehydration).

Symptoms concerning chest and abdomen

(5) Difficulty breathing.
(6) Feeling of choking.
(7) Chest pain or discomfort.
(8) Nausea or abdominal distress (e.g. churning in stomach). Symptoms concerning brain and mind
(9) Feeling dizzy, unsteady, faint or light-headed.
(10) Feelings that objects are unreal (derealization), or that one's self is distant or "not really here" (depersonalization).
(11) Fear of losing control, going crazy, or passing out.
(12) Fear of dying.

General symptoms

(13) Hot flushes or cold chills.
(14) Numbness or tingling sensations.

Symptoms of tension

(15) Muscle tension or aches and pains.
(16) Restlessness and inability to relax.
(17) Feeling keyed up, or on edge, or of mental tension.
(18) A sensation of a lump in the throat, or difficulty with swallowing.

Other non-specific symptoms

(19) Exaggerated response to minor surprises or being startled. (20) Difficulty in concentrating, or mind going blank, **because of worrying or anxiety.**
(21) Persistent irritability.
(22) Difficulty getting to sleep because of worrying.

c. The disorder does not meet the criteria for panic disorder, phobic anxiety disorders, obsessive-compulsive disorder or hypochondriacal disorder

d. Most commonly used exclusion criteria: not sustained by a physical disorder, such as hyperthyroidism, an organic mental disorder or psychoactive substance-related disorder, such as excess consumption of amphetamine-like substances, or withdrawal from benzodiazepines.

Drug treatment:

The drugs prescribed for the GAD patients include selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, tricyclic anti-depressant, benzodiazepines and sometimes even low dose of anti-psychotics.[44] SSRIs are considered to be the first line of treatment for GAD because of their efficacy and tolerability. However they have the propensity to exacerbate anxiety in the early stages of the treatment. Therefore it is best to start with low dose and titrate it to recommended levels. Benzodiazepines are the other drugs which are most frequently prescribed. Their side effects include tremors, nausea, headache, agitation and sleep disturbance.[44] Tolerance and dependence have been reported with more than two weeks of benzodiazepines therapy. Due to the potential of dependence, benzodiazepines are not recommended as the first line agents.[44] Non-benzodiazepines anxiolytics, like Buspirone, also established efficacy in the management of GAD.[44]

CONCLUSION

GAD is a complex psychiatric disorder with high prevalence rates. There are underlying genetic risk factors which have been focus of research in recent times. A substantial body of literature examines the neurobiological changes associated with the GAD. While effective therapies for the management of GAD exist their provision in the resource-constrained settings is a great challenge. More research is needed in order to understand the epidemiological risk factors and neurobiological underpinning of the GAD.

REFERENCES

1. American Psychiatric A. Diagnostic and statistical manual of mental disorders: DSM-IV-TR: American Psychiatric Publishing, Inc.; 2000.
2. Ruscio AM, Chiu WT, Roy-Byrne P, et al. Broadening the definition of generalized anxiety disorder: effects on prevalence and associations with other disorders in the National Comorbidity Survey Replication. Journal of anxiety disorders. 2007;21(5): 662- 76.
3. Merikangas KR, He J-P, Brody D, Fisher PW, Bourdon K, Koretz DS. Prevalence and treatment of mental disorders among US children in the 2001â€"2004 NHANES. Pediatrics.125(1): 75- 81.
4. Merikangas KR, He MJ-p, Burstein M, et al. Lifetime prevalence of mental disorders in US adolescents: Results from the National Comorbidity Study Adolescent Supplement (NCS-A). Journal of the American Academy of Child and Adolescent Psychiatry.49(10):980.
5. Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU. Twelveâ€ month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. International journal of methods in psychiatric research. 21(3):169-184.
6. Lieb R, Becker E, Altamura C. The epidemiology of generalized anxiety disorder in Europe. European Neuropsychopharmacology. 2005;15(4):445-452.
7. Nilsson J, Ã-stling S, Waern M, et al. The 1-Month Prevalence of Generalized Anxiety Disorder According to DSM-IV, DSM-V, and ICD-10 Among Nondemented 75-Year-Olds in Gothenburg, Sweden. The American Journal of Geriatric Psychiatry.20(11):963-972.
8. Munk-JÃ¸rgensen P, Allgulander C, Dahl A, et al. Prevalence of generalized anxiety disorder in general practice in Denmark, Finland, Norway, and Sweden. Psychiatric Services. 2006;57(12):1738-1744.
9. Qin X, Phillips MR, Wang W, et al. Prevalence and rates of recognition of anxiety disorders in internal medicine outpatient departments of 23 general hospitals in Shenyang, China. General hospital psychiatry.32(2):192.
10. Wittchen H-U, Hoyer Jr. Generalized anxiety disorder: nature and course. Journal of Clinical Psychiatry. 2001;62:15-21.
11. Sahoo S, Khess CRJ. Prevalence of depression, anxiety, and stress among young male adults in India: A dimensional and categorical diagnoses based study. The Journal of nervous and mental disease.198(12):901-904.
12. Mohammadi M-R, Davidian H, Noorbala AA, et al. An epidemiological survey of psychiatric disorders in Iran. Clinical Practice and Epidemiology in Mental Health. 2005;1(1):16.
13. Ali BS, Rahbar MH, Tareen AL, Gui A, Samad L, Naeem S. Prevalence of and factors associated with anxiety and depression among women in a lower middle class semi-urban community of Karachi, Pakistan. Prevalence. 2002.
14. Watkins ER. Constructive and unconstructive repetitive thought. Psychological bulletin. 2008;134(2):163.
15. Nakazato K, Shimonaka Y. The Japanese state trait anxiety inventory: Age and sex differences. Perceptual and Motor Skills. 1989;69(2) :611- 617.
16. Wittchen HU, Zhao S, Kessler RC, Eaton WW.

DSM-III-R generalized anxiety disorder in the National Comorbidity Survey. Archives of General Psychiatry. 1994;51(5):355.
17. Scott KM, Wells JE, Angermeyer M, et al. Gender and the relationship between marital status and first onset of mood, anxiety and substance use disorders. Psychological Medicine. 2010;40(09):1495-1505.
18. Mirza I, Jenkins R. Risk factors, prevalence, and treatment of anxiety and depressive disorders in Pakistan: systematic review. Bmj. 2004;328(7443):794.
19. Grant BF, Goldstein RB, Chou SP, et al. Sociodemographic and psychopathologic predictors of first incidence of DSM-IV substance use, mood and anxiety disorders: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. Molecular psychiatry. 2008;14(11):1051-1066.
20. O'Brien CP. Benzodiazepine use, abuse, and dependence. J Clin Psychiatry. 2005;66(suppl 2):28-33.
21. Mathew A, Pettit J, Lewinsohn P, Seeley J, Roberts R. Co-morbidity between major depressive disorder and anxiety disorders: shared etiology or direct causation? Psychological Medicine. 2011;41(10):2023-2034.
22. La Greca AM, Harrison HM. Adolescent peer relations, friendships, and romantic relationships: do they predict social anxiety and depression? Journal of Clinical Child and Adolescent Psychology. 2005;34(1):49-61.
23. Khan H, Kalia S, Itrat A, et al. Prevalence and demographics of anxiety disorders: a snapshot from a community health centre in Pakistan. Annals of general psychiatry. 2007;6(1):30.
24. Jenaro C, Flores N, Gómez-Vela M, González-Gil F, Caballo C. Problematic internet and cell-phone use: Psychological, behavioral, and health correlates. Addiction research & theory. 2007;15(3):309-320.
25. Wittchen HU. Generalized anxiety disorder: prevalence, burden, and cost to society. Depression and anxiety. 2002;16(4):162-171.
26. Arikian SR, Gorman JM. A review of the diagnosis, pharmacologic treatment, and economic aspects of anxiety disorders. Primary care companion to the Journal of clinical psychiatry. 2001;3(3):110.
27. Greenberg PE, Sisitsky T, Kessler RC, et al. The economic burden of anxiety disorders in the 1990s. Journal of Clinical Psychiatry. 1999.
28. Pesa J, Lage MJ. The medical costs of migraine and comorbid anxiety and depression. Headache: The Journal of Head and Face Pain. 2004;44(6):562-570.
29. Lohoff FW, Narasimhan S, Rickels K. Interaction between polymorphisms in serotonin transporter (SLC6A4) and serotonin receptor 2A (HTR2A) genes predict treatment response to venlafaxine XR in generalized anxiety disorder. The Pharmacogenomics Journal.
30. Smith KS, Rudolph U. Anxiety and depression: Mouse genetics and pharmacological approaches to the role of GABA< sub> A</sub> receptor subtypes. Neuropharmacology.62(1):54-62.
31. Hettema JM, Kettenmann B, Ahluwalia V, et al. Pilot multimodal twin imaging study of generalized anxiety disorder. Depression and anxiety.29(3):202-209.
32. Hedman E, Andersson E, LjÃ³tsson B, et al. Clinical and genetic outcome determinants of Internetâ€and groupâ€based cognitive behavior therapy for social anxiety disorder. Acta Psychiatrica Scandinavica.126(2):126-136.
33. Narasimhan S, Aquino TD, Multani PK, Rickels K, Lohoff FW. Variation in the catechol-O methyltransferase (COMT) gene and treatment response to venlafaxine XR in generalized anxiety disorder. Psychiatry research.198(1):112-115.
34. Knappe S, Beesdoâ€ Baum K, Nocon A, Wittchen hu. reâ€examining the differential familial liability of agoraphobia and panic disorder. Depression and anxiety.29(11):931-938.
35. Scaini S, Ogliari A, Eley TC, Zavos H, Battaglia M. genetic and environmental contributions to separation anxiety: a metaâ€ analytic APPROACH TO TWIN DATA. Depression and anxiety.29(9):754-761.
36. Yassa MA, Hazlett RL, Stark CEL, Hoehn-Saric R. Functional MRI of the amygdala and bed nucleus of the stria terminalis during conditions of uncertainty in generalized anxiety disorder. Journal of psychiatric research.
37. Damsa C, Kosel M, Moussally J. Current status of brain imaging in anxiety disorders. Current opinion in psychiatry. 2009;22(1):96-110.
38. De Bellis MD, Casey BJ, Dahl RE, et al. A pilot study of amygdala volumes in pediatric generalized anxiety disorder. Biological psychiatry. 2000;48(1):51-57.
39. Strawn JR, Wehry AM, Chu WJ, et al. neuroanatomic abnormalities in adolescents with generalized anxiety disorder: a voxelâ€based morphometry study. Depression and anxiety.
40. Schienle A, Ebner F, SchÃ€fer A. Localized gray matter volume abnormalities in generalized anxiety

disorder. European archives of psychiatry and clinical neuroscience.261(4):303-307.
41. Mathew SJ, Mao X, Coplan JD, et al. Dorsolateral prefrontal cortical pathology in generalized anxiety disorder: a proton magnetic resonance spectroscopic imaging study. American Journal of Psychiatry. 2004;161(6):1119-1121.
42. Brambilla P, Como G, Isola M, et al. White-matter abnormalities in the right posterior hemisphere in generalized anxiety disorder: a diffusion imaging study. Psychological Medicine.42(02):427-434.
43. Roy AK, Fudge JL, Kelly C, et al. Intrinsic functional connectivity of amygdala-based networks in adolescent generalized anxiety disorder. Journal of the American Academy of Child and Adolescent Psychiatry.52(3):290.