



ANXIETY DISORDERS IN WOMEN:



Authors:

M. Katherine Shear, MD1 Marylene Cloitre, PhD2 Daniel Pine, MD3 Jerilyn Ross, MS, LICSW4

Dr. Shear has an MD from Tufts University and is Professor in the Department of Psychiatry at the University of Pittsburgh in Pittsburgh, Pennsylvania.

Dr. Cloitre has a PhD from Columbia University and is Director of the Institute for Trauma and Stress at the NYU Child Study Center, New York, New York.

Dr. Pine has an MD from the University of Chicago, Pritzker School of Medicine and is Chief of Developmental Studies, Mood & Anxiety Disorders Program, National Institute of Mental Health-Intramural Research Program in Rockville, Maryland.

Ms. Ross has an MA degree from the New School for Social Research Graduate Faculty of Political and Social Science and is President and CEO of the Anxiety Disorders Association of America and Director of The Ross Center for Anxiety & Related Disorders in Washington, DC.

Acknowledgements

This conference, which was convened by the Women's Health Initiative of the Anxiety Disorders Association of America (ADAA), was supported by an unrestricted educational grant from the members of the Corporate Advisory Council of ADAA, including Eli Lilly and Company, Forest Laboratories, Inc, Pfizer Inc, Solvay Pharmaceuticals, Wyeth Pharmaceuticals, and GlaxoSmithKline.

Editorial support and manuscript development provided by Sally K. Laden, MSE Communications.

For additional information or to order copies, contact the ADAA at: Anxiety Disorders Association of America 8730 Georgia Avenue, Suite 600, Silver Spring, Maryland 20910 Phone: 240-485-1001 Web address: www.adaa.org

Copyright 2005 Anxiety Disorders Association of America All rights reserved. Printed in the United States of America

Introduction

Anxiety disorders are common and disabling. During their lifetimes, one out of every four Americans will fulfill diagnostic criteria for at least one anxiety disorder. Women are at increased risk for anxiety disorders, and developmental, societal, and reproductive factors are believed to contribute to the preponderance of this vulnerability.² Anxiety disorder research in general is moving forward at a robust pace. However, research on sex differences in anxiety has lagged considerably, and little data are available to guide prevention, treatment, and public health policy efforts that are specifically focused on women and girls. The lack of information about the origins of sex differences in anxiety disorders is serious and needs to be rectified.

The Anxiety Disorders Association of America (ADAA) is the only national, nonprofit professional and consumer organization focused exclusively on the diagnosis, prevention, and treatment of anxiety disorders. In recognition of the need to advance the state of knowledge about anxiety disorders in women and girls, the Women's Health Initiative of the ADAA sponsored a two-day conference on

November 19-20, 2003 in Chantilly, Virginia. The objectives of this conference were to increase awareness of anxiety disorders in women and girls and to identify a research agenda that will further the recognition, prevention, and treatment of anxiety disorders in this population. The conference included basic and clinical researchers in psychiatry, psychology, women's health, healthcare policy, and patient advocacy. Conference members listened to presentations and participated in workgroups that drafted position statements on research needs related to mechanisms of sex differences in anxiety disorders, clinical importance of sex differences, the relationship of anxiety disorders to the reproductive lifecycle and women's health, and public health issues related to anxiety disorders in women. Workgroup leaders presented draft position statements that were considered and debated by all conference members. This position paper reflects the presentations and deliberations from the ADAA conference.

Clinical Importance of Sex Differences



A large and compelling body of evidence from general population surveys confirms that each of the DSM IV anxiety disorders is more common in females than in males.^{1,3-6}

During their lifetimes, women are twice as likely as men to have panic disorder (5.0% versus 2.0%), agoraphobia (7.0% versus 3.5%), PTSD (10.4% versus 5.0%), or GAD (6.6% versus 3.6%). Social anxiety disorder (15.5% versus 11.1%) and OCD (3.1% versus 2.0%) also are more common in females than in males, but differences in prevalence rates are less pronounced. 1,7

MORBIDITY

The personal and societal burden of anxiety disorders is well-established. Anxiety disorders are strongly associated with comorbid depression, alcohol/drug abuse, functional impairment, poor quality of life, suicidality, and excessive utilization of healthcare resources. There is a small body of literature documenting sex differences in secondary comorbidities. Women with PTSD may be at increased risk of cocaine use and alcohol dependence

compared with men with PTSD.¹³ The secondary social consequences for women with anxiety disorders have been considered in the National Comorbidity Survey (NCS) database. Anxiety disorders are more common in females than in males who failed to complete high school (5.4% versus 2.9%) or college (3.0% versus 1.9%).14 Divorce rates for women with GAD, panic disorder, or social anxiety disorder are lower than in men with these disorders.¹⁵ Anxiety disorders are associated with teenage pregnancy, but are weaker predictors of teenage parenthood than substance abuse disorders or conduct disorder. 16

Research is needed to address gaps in this body of research. For example, most studies examining anxiety-associated morbidity rely on cross-sectional or retrospective data, which are vulnerable to various biases. Prospective studies are needed. Because sex differences in anxiety

prevalence emerge prior to adolescence, there is a particularly pressing need for prospective, longitudinal studies that follow boys and girls into adulthood. Findings from available prospective studies have noted a greater long-term morbidity in girls, relative to boys, with anxiety disorders, ¹⁷ though not all studies note such sex differences. ¹⁸

RISK FACTORS

Very little is known about antecedent risk factors for anxiety disorders in girls and women. Seminal findings from a female twin registry suggest that genetic factors are an important hazard for anxiety disorders in women. ¹⁹ Familial environment also may contribute to increased risk,

especially for GAD.²⁰ Generalized anxiety disorder is of interest because of findings that it shares a common genetic pathway with major depression in women.¹⁹ An emerging literature offers compelling evidence that early life adversity, such as childhood sexual or physical abuse, predisposes to the development of anxiety disorders later in life. 21,22 Women who were sexually abused as children appear to be at increased risk of adult-onset PTSD²³ and panic disorder.24 Similarly, when assessed as adults, adolescent girls who had formerly been exposed to stress exhibit a greater risk for symptoms of GAD than adolescent boys.²⁵



Women who were sexually abused as children appear to be at increased risk of adult onset PTSD and panic disorder.

CLINICAL PRESENTATION

Sex differences in the clinical presentation of anxiety disorders are recognized, and panic disorder is the best studied illness in this regard. Compared with men, panic disorder in women tends to be more severe and associated with higher rates of significant comorbidity, such as agoraphobia, GAD, and somatization disorder.^{26,27} Long-term follow-up data from the Harvard/Brown Anxiety Research Program (HARP) study confirm that remission rates for panic disorder and panic disorder with agoraphobia were similar for men and women. However, women with uncomplicated panic disorder experienced three-fold higher rates of relapse.²⁸

Posttraumatic stress disorder is a particularly salient disorder to consider in the context of sex differences. Rates of PTSD from the National Comorbidity Survey (NCS) are higher in women (20.4%) than in men (8.2%), and the nature of the traumatic event may account in part for increased risk for PTSD among women.²⁹ Though assaultive violence is experienced more often by men than by women, rates of PTSD following a personal attack are 21.3% for women versus 1.8% for men. Men and women develop PTSD at approximately similar rates (ie, 65% and 46%, respectively) following

exposure to a natural disaster (e.g., earthquake), which suggests that women who experience personal violence are more vulnerable to PTSD than are men. Moreover, women with PTSD are more likely to present with symptoms of numbing and avoidance, which is in contrast to men, who often exhibit irritability and difficulties with impulse control. 40

Compared with panic disorder and PTSD, less is known about sex differences in the clinical presentation of other anxiety disorders. Though the lifetime prevalence of social anxiety disorder in women (15.5%) is not markedly greater than in men (11.1%), genetic transmission may contribute to the increased risk in women.²⁶ Women with social anxiety disorder also may be at increased risk of agoraphobia.²⁶ The HARP study found that women with social anxiety disorder and a history of suicide attempts tend to have a particularly unremitting course of illness.²⁸ Thus, limited data suggest that social anxiety disorder in women may be characterized by heritability, greater comorbidity, and a more severe illness course. Certain clinical domains of OCD exhibit sex differences, with females being more likely to exhibit cleaning/contamination or aggression/ checking compulsions, comorbid depression or an eating disorder, and a less severe clinical course.^{26,31}

TREATMENT

There is a marked paucity of data about sex differences in treatment seeking for anxiety disorders.³² Clinical experience suggests that women are more likely to seek treatment for anxiety than men. However, it is believed that there are significant barriers to treatment for women. For example, women generally assume the bulk of childrearing responsibility, which may pose difficulties when seeking therapy if childcare is not available or affordable. Anxiety symptoms may not be recognized or accepted in girls because of gender-specific role expectations, which may normalize symptoms of worrying, shyness, or fear. Other barriers to treatment for women may include cost of therapy, lack of insurance for mental health care, stigma associated with a psychiatric diagnosis, and unavailable or inaccessible healthcare services.

Potential sex differences in anxiety disorder treatment response is an important area of consideration. However, to date, little attention has been paid to sex differences in treatment outcomes. There is some suggestion of sex differences for adults in response to treatment with the selective serotonin reuptake inhibitors (SSRIs), but this favors women. In an unpublished post-hoc analysis³⁰ of a PTSD treatment trial,³³ women who were treated with sertraline achieved greater improvement on PTSD symptom scores than men. Though sex differences for factors that are associated with pharmacokinetic and pharmacodynamic properties are recognized (e.g., fat composition, gastric emptying time, protein binding, cytochrome P450 enzyme activity), the contribution of these differences to medication response in the treatment of anxiety disorders is not known.²⁶

Posttraumatic stress disorder is a particularly salient disorder to consider in the context of sex differences.

RESEARCH PRIORITIES

Descriptive studies of clinical and community samples:

- Describe course of anxiety disorders during reproductive transitions across the lifespan;
- Identify and elucidate sexspecific factors in the etiology and pathophysiology of anxiety disorder presentation, course, and treatment effects;
- Improve assessment, recognition, and diagnosis of anxiety disorders in young girls;
- Longitudinally assess genderrelevant vulnerability and resilience factors.

Symptoms may not be recognized in girls because of gender-specific role expectations.

Prevention and treatment studies:

 Conduct large-scale, longitudinal studies of early-onset anxiety disorders, stratified by sex, to determine impact of preventive

- and/or therapeutic interventions on illness course, comorbid conditions, and functional impairment. Focus on middle school and high school populations to measure effect of prevention/intervention on school performance, self-esteem, and other behavioral indicators;
- Conduct studies in high-risk populations, such as girls and women with histories of early-life adversity, pubertal girls with emergent low selfesteem, pregnant women with anxiety disorders;
- Identify mothers with anxiety disorders in primary care and pediatric healthcare settings in order to:
 - Enhance parenting skills;
 - Educate and intervene to improve diagnosis and treatment of mothers and prevent adverse sequelae in their children.
- Conduct effectiveness trials in women with anxiety disorders and secondary comorbidity (e.g., mood or anxiety disorders, substance use disorders) with a focus on female-specific functional outcomes.

Mechanisms of Sex Differences in Anxiety Disorders



Despite documentation of sex differences in some anxiety disorders, there is little convincing evidence for any established mechanism underlying these differences.

In this context, mechanisms can be defined as any factor that can alter anxiety-related behavior. There is a remarkable paucity of established animal models that have investigated potential mechanisms underlying sex differences in anxiety. It is important for research on mechanisms of sex differences in anxiety disorders to focus on early development. Several questions are therefore relevant with regard to identifying research priorities. First, are there constitutional differences that predispose males and females to a differential expression or experience of anxiety that are subsequently amplified or suppressed by experience? Second, are there specific lifespan modulators that alter vulnerability to anxiety at different developmental stages that are separate from inborn risks for anxiety?

It is unlikely that a single mechanism or even a unique constellation of factors will account for sex differences in anxiety at all life stages. Examining several distinct stages in the life cycle during which sex differences occur could serve as starting points for the exploration of potential mechanisms. Anxiety sympoms as well as manifestations of anxiety, such as autonomic arousal, could be studied during childhood developmental epochs, including the neonatal and very early life period, pre-puberty, peri-puberty, and post-puberty adulthood. Findings could serve as starting points for the exploration of potential mechanisms that might account for sex-related differences.

Behavioral inhibition in infants and very young children is associated with anxiety later in life.^{34,35} There has been a suggestion that adolescent girls who were behaviorally inhibited as toddlers may be more prone to generalized social anxiety disorder than boys.³⁶ However, studies of temperament in early life do not strongly support a role for sex differences in the relationship of behavioral inhibition to anxiety.³⁷

On the other hand, there is some evidence of sex differences in anxiety disorders and anxiety-like symptoms in pre-pubertal children. Obsessive compulsive disorder is more common in pre-pubertal males, but generally does not emerge in females until young adulthood.³⁸ Separation anxiety disorder is twice as prevalent in girls as in boys.¹⁷ Elementaryschool age girls are more likely to exhibit fearful behavior, whereas boys are more likely to exhibit impulsive and low helpfulness behaviors.³⁹ In addition, negative affect is observed more often in girls than in boys.⁴⁰ The development of first-episode panic attacks is more common in pubertal girls compared with boys. 41,42 Mechanisms for these differences have not been elucidated.

There is a similar deficiency of data related to mechanisms for sex differences in adults with anxiety disorders, though some early findings might guide future research. Among adults, there is evidence for a sexspecific pattern of reactivity to socially threatening stimuli. For example, women who are exposed to assaultive trauma are more likely to develop PTSD than men.^{5,29} Brain imaging studies suggest that these differences may relate to divergence in amygdala or prefrontal cortex functioning of males compared to females.43 Anxiety symptoms may worsen during the late luteal phase of the menstrual cycle in some women.⁴⁴ The literature suggests that panic disorder may be exacerbated or ameliorated during pregnancy or the postpartum period.⁴⁷

Examining several distinct stages in the life cycle during which sex differences occur could serve as starting points for the exploration of potential mechanisms.



RESEARCH PRIORITIES

Studies of anxiety during periods of the life cycle associated with robust hormonal changes in women:

- Longitudinally assess changes in brain structure and function and in measurable behaviors focusing on vulnerable periods in the female life cycle;
- Investigate potential neurobiological changes associated with changes in sex hormones;
- Prospectively examine changes in women during adrenarche, gonadal puberty, menstrual cycle, pregnancy, post-partum, menopause, and hormone replacement therapy.

Studies of contextual or interpersonal factors that may affect anxiety:

 Describe features of interpersonal functioning during important periods of the life cycle, such as mother-infant

Obsessive compulsive disorder is more common in pre-pubertal males, but generally does not emerge in females until young adulthood.

- attachment, weaning, schoolbased social relationships, dating, and transition to independent living, marriage, child-rearing, senescence, and retirement;
- Identify and track potentially pathogenic interpersonal experiences, including trauma, familial factors (e.g., violence, parental loss or conflict, sibling interactions), peer relationships (e.g., bullying, excessive shyness), and response to pubertal changes.

Studies of sex differences in cognitive and emotional processing in community samples and clinical populations:

- Incorporate neuroimaging techniques and experimental and self-report symptom and other psychological measures in epidemiological surveys;
- Focus on sex-specific mechanisms for threat appraisal, response to anxiogenic cues and capacity for emotion regulation across the lifespan.

Studies of sex differences in animal models of anxiety:

- Incorporate examination of sex differences into studies of fear and anxiety; stratify these studies by sex;
- Identify and validate sex-relevant contextual measures when studying anxiety in rodents;

 Conduct non-human primate studies of sex differences in anxiety.

Include integrative approaches to anxiety disorder studies:

 Recognize that mechanisms underlying sex differences in anxiety are likely to be multi-determined; Support collaboration across the multiple domains associated with sex differences in anxiety disorders.

Study anxiety in congenital syndromes (e.g., congenital adrenal hyperplasia, fragile *X* syndrome, androgen insensitivity syndrome) likely to elucidate sex-relevant mechanisms.

Reproductive Lifespan Issues



A woman's reproductive life is characterized by marked fluctuations in levels of estrogen and progesterone, which have the potential to modulate anxiety.

However, effects of reproductive hormones on anxiety are complex, and this remains an understudied area with disappointing levels of collaboration between researchers interested in anxiety disorders and those studying reproductive functioning.

PUBERTY

Unlike anxiety disorders, depression is not prevalent in young children, and sex differences in depression do not occur until adolescence, at which point girls are twice as likely to have depression as boys. 48,49 In contrast, anxiety disorders are prevalent in prepubertal children. There is an early female preponderance of some anxiety disorders, and the influence of pubertal status or hormonal factors on the prevalence of anxiety disorders in males and females remains unclear. Findings of sex differences in childhood anxiety disorders differ according to the disorder under study. Results from

one large community sample of children with a variety of different anxiety disorders indicate that by age six, girls are twice as likely as boys to have developed an anxiety disorder and that the disorder will be more severe in girls than in boys. ⁵⁰ Separation anxiety disorder is more prevalent in girls. However, not all anxiety disorders are the same. For example, boys are more likely to first develop OCD before puberty than are girls, but after the age of 20, females are at higher risk of incident OCD than males. ³⁸

PREMENSTRUAL Dysphoric Disorder

Some women with PMDD have comorbid anxiety disorders, with social anxiety disorder and specific phobia being the most common. ^{51,52} Existing mood and anxiety disorders often are exacerbated during the late luteal phase, and evidence for premenstrual worsening of symptoms has been

suggested by the findings of prospective^{52,53} and retrospective^{54,55} studies in women with GAD, panic disorder, OCD, or social anxiety disorder. Anxiety symptoms, such as fear, worry, or nervousness, are not consistently observed in PMDD, although there may be increased premenstrual vulnerability to a panic-like state characterized by anticipatory tension and irritability.

PREGNANCY

Anxiety disorders represent a clinical challenge in the pregnant woman. However, again, too little is known about anxiety during pregnancy, the postpartum period, and lactation. There is evidence that stress responses are blunted during pregnancy, particularly in the third trimester. ^{56,57} Yet little is known about the interaction of perinatal

fluctuations in estrogen and progesterone levels and symptoms of anxiety disorders, or about the effect of pregnancy on efficacy of anxiolytic medications.

Increased anxiety symptoms during pregnancy have been documented a study that employed the Speilberger State-Trait Anxiety Inventory.58 Emerging data also suggest that anxiety symptoms occurring during pregnancy may be associated with perinatal complications, such as preeclampsia, premature rupture of membranes, cesarean section, and fetal complications.⁵⁹ In a study of pregnant women with PTSD, findings indicated increased risk of ectopic pregnancy, miscarriage, hyperemesis, preterm contractions, and excessive fetal growth. 60 Such results have implications for perinatal

There is evidence that stress responses are blunted during pregnancy, particularly in the third trimester.



management, fetal outcome, and childhood development and warrant further study.

In general, it appears that pregnancy is not protective against all anxiety disorders. However, results of studies that were mostly retrospective in design suggest that pregnancy has a

In general, it appears that pregnancy is not protective against all anxiety disorders.

variable effect on panic disorder and OCD. Of 215 pregnancies evaluated in one systematic review, ⁴⁶ panic symptoms improved in 41% of women, and 38% experienced either new-onset panic disorder or exacerbation of existing illness. Similar findings of a variable effect of pregnancy on the course of anxiety have been reported for women with OCD. ⁵⁵

POSTPARTUM PERIOD

New mothers may be particularly vulnerable to anxiety disorders. Though study samples are small, it appears that panic disorder^{47,61,62} and OCD^{55,63,64} are exacerbated or emergent during the postpartum period in many women. Intrusive obsessions related to harming the newborn are common in women with postpartum OCD.⁵⁹ The development of PTSD after childbirth has been observed to occur in 1.7% to 5.6% of women who experienced traumatic deliveries.^{65,66}

LACTATION

Emerging data suggest that breastfeeding may offer some protection against postpartum anxiety by providing a gradual physiological transition from the pregnant to the non-pregnant state.⁶⁷ Findings from animal studies demonstrate increased levels of the anxiolytic neurotransmitter, y-aminobutyric acid (GABA), during lactation.⁶⁸ In studies of new mothers, lactating women exhibited decreased hypothalamic-pituitary-adrenal (HPA) axis and adrenergic stress responses compared with bottlefeeding women. 69,70 There is crosssectional, naturalistic evidence that breastfeeding women have fewer anxiety symptoms compared with bottle-feeding women. 71-73

PERIMENOPAUSE

Anxiety symptoms are anecdotally reported to be elevated in perimenopausal women, but there are no published data to confirm this. A validated 12-item menopausal symptom list has been developed that measures psychological, somatic, and vasomotor symptoms associated with the perimenopause,⁷⁴ and studies of anxiety during this period are ongoing. Ovarian aging is a measurable parameter that can be detected a decade or more before the onset of menopause, which is encouraging with regard to the possibility of conducting longitudinal studies.

RESEARCH PRIORITIES

Studies of menarche and PMDD:

- Document the incidence and course of anxiety disorders across menarche;
- Determine whether anxiety disorders comprise risk factors

Anxiety symptoms
are anecdotally reported
to be elevated in
perimenopausal women,
but there are no published
data to confirm this.

- for infertility and/or functional amenorrhea;
- Examine the effect of menstruation onset, offset, and cycling (ie, menarche, normal menses, perimenopause) on symptoms of anxiety disorders;
- Understand the therapeutic mechanisms associated with PMDD treatment (e.g., rapid onset/offset of therapeutic response to SSRIs and interaction with anxiolytic neurosteroids).

Studies of pregnancy, postpartum, and lactation:

- Determine whether anxiety disorders, especially PTSD, are risk factors for hyperemesis gravidarum, preterm labor, and other pregnancy complications;
- Determine whether women with anxiety disorders are at risk for pregnancy loss, including miscarriage, stillbirth, and fetal reduction;
- Measure the severity, symptom profile, and fluctuations of anxiety during pregnancy and postpartum
- Study the longitudinal course of anxiety disorders during pregnancy and postpartum (including lactation);

Studies of menarche and PMDD: Document the incidence and course of anxiety disorders across menarche.

- Explore the possible existence of reproductive event-specific excessive anxiety responses (e.g., a pregnancy-related anxiety syndrome);
- Conduct treatment studies of women with perinatal anxiety disorders.

Public Health Implications



The preponderance of anxiety disorders in women represents a public health concern of great importance.

Twenty-five percent of all adults will experience an anxiety disorder in their lifetime, and women bear a disproportionate share of this burden in terms of prevalence, disability, and treatment costs. The indirect costs associated with anxiety disorders, such as impaired vocational productivity and disrupted interpersonal functioning, may also be greater among women. Smoking, substance use, and other adverse health behaviors have a significant negative impact on women's health and increase the cost burden of anxiety disorders. Because women are often primary caregivers, the costs of untreated and unrecognized anxiety disorders extend beyond individual women to their children, significant others, and extended families in ways that may not occur for men.

Barriers to the detection and effective treatment of anxiety disorders in women cross multiple domains and are related to stigma, unavailability of healthcare services, ethnic and cultural factors, and socioeconomic status. Access to treatment and parity are especially important issues for women. Medical and psychiatric comorbidity may be different in women than in men and may likely play an important role in the recognition and treatment of anxiety disorders. There may be differences in response to behavioral and pharmacological treatment interventions between men and women, or differences among women at different points in the reproductive cycle. Therefore, treatment studies need to be conducted and stratified by sex. Sexual functioning merits special attention as a health outcome associated with anxiety disorders.

A high and sustained level of public and professional awareness is needed if significant, emergent findings related to anxiety disorders in women and girls are to remain a priority for healthcare policy makers. Cost data must be collected so that the current and future economic burden of

undiagnosed and inadequately treated anxiety disorders in girls and women can be documented and used to persuade policy makers of the importance of this issue. A broadreaching public education campaign that features prominent and effective spokespersons and utilizes the full spectrum of mass media, including but not limited to television, print media, radio, schools, and the internet, will advance this agenda. Public awareness campaigns should reach a wide demographic with the message that anxiety disorders are real illnesses that are prevalent, disabling, recognizable, linked to suicide and substance abuse, and highly treatable.

Programs that increase awareness of anxiety disorders in women also must target healthcare providers. The anxiety disorders research community should increase their interaction with the Centers for Disease Control and Prevention by lobbying for inclusion of anxiety-related questions and diagnoses in behavioral risk factor surveillance data. In addition, the research community should lobby the National Institute of Child Health and Human Development to increase funding for studies of the role of anxiety disorders in healthy development and to include anxiety measures in their ongoing longitudinal study of pregnant women.



Medical and psychiatric comorbidity may be different in women than in men and may likely play an important role in the recognition and treatment of anxiety disorders.

Clinicians and researchers need to increase their efforts to deliver scientific and continuing medical education presentations and publish original data and systematic reviews on the public health consequences of anxiety disorders in women and girls. Inclusion of measures of anxiety disorders and other mental illnesses in ongoing women's health studies, such as the Nurses' Health Study and the Women's Health Initiative Study, will collect valuable data.

RESEARCH PRIORITIES

- Access and re-analyze available datasets to determine sex differences in the onset, course, comorbidities, functional disability, and healthcare resource utilization for anxiety disorders in women and determine the gaps in the literature that merit further investigation. Though there are many studies of the epidemiology, biology, treatment, and healthcare resource utilization of anxiety disorders, the data has rarely been disaggregated by sex and comprehensively reviewed;
- Document the economic burden of anxiety disorders in women, including direct treatment-related costs and indirect costs associated with

Programs that increase awareness of anxiety disorders in women also must target healthcare providers.

truncated education, poor occupational function, impaired role functioning and interpersonal relationships, and suicidal behavior;

- Study methods of effective case finding for anxiety disorders in girls and young women;
- Identify aspects of women's unique biology that impact the treatment of anxiety disorders and affect associated health consequences;
- Study the relationship between anxiety disorders and illnesses that may be particularly common among women, such as fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and multiple chemical sensitivity and document the costs associated with these conditions;

- Design and test economically feasible and sustainable public health models that prevent, detect, and treat anxiety disorders in women and increase access to care;
- Identify aspects of the patient, provider, healthcare system, and healthcare environment that are associated with best practices in the detection and treatment of anxiety disorders.

Conclusions



Despite a large and growing body of literature on anxiety disorders in general, the available data that specifically relates to women and girls falls short of informing aspects of diagnosis, treatment, and prevention that may entail sex differences.

The study of anxiety disorders in women is in its infancy. In response to the multiple unmet research needs, participants in this conference, which was sponsored by the Women's Health Initiative of the ADAA, issued a call to action by outlining a research agenda that focuses on several key areas:

- Document the social costs and economic burden of anxiety disorders in women;
- Identify sex-specific developmental risk factors to understand the temporal development of anxiety disorders and to characterize vulnerability and resilience;
- Develop animal models of anxiety in females to better understand mechanisms of sex differences in anxiety disorders;

- Characterize fluctuations in anxiety symptoms and course of anxiety disorders during the reproductive life cycle (menarche, the menstrual cycle, childbearing events, and the perimenopause);
- Understand the bidirectional relationship between anxiety and reproductive functioning, including the potential role of anxiety as a moderator of reproductive life cycle events and the potential role of reproductive physiology in determining the course of anxiety disorders;
- Determine whether there is a unique clinical presentation of some anxiety disorders in girls and women and apply this knowledge to improved preventive and therapeutic interventions;

- Design and study 'best practice' models to optimize quality of care for girls and women with anxiety disorders;
- Develop effective educational campaigns that target the public and healthcare professionals;
- Foster collaboration between anxiety disorder and women's health researchers and between the research community, clinicians, medical educators, patient advocates, healthcare policy makers, and insurers.



Determine whether there is a unique clinical presentation of some anxiety disorders in girls and women.

References

- 1. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry*. 1994; 51:8-19.
- 2. Pigott TA. Anxiety disorders in women. *Psychiatr Clin N Am.* 2003; 26:621-672.
- 3. Eaton WW, Kramer M, Anthony JC, Dryman A, Shapiro S, Locke BZ. The incidence of specific DIS/DSM-III mental disorders: data from the NIMH Epidemiologic Catchment Area program. *Acta Psychiatr Scand.* 1989; 79:163-178.
- 4. Gater R, Tansella M, Korten A, et al. Sex differences in the prevalence and detection of depressive and anxiety disorders in general health care settings. Report from the World Health Organization collaborative study on psychological problems in general health care. *Arch Gen Psychiatry*. 1998; 55:405-413.
- Kessler RC, Sonnega A, Bromet E, et al. Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry. 1995; 52:1048-1060.
- 6. Weissman MM, Bland RC, Canino GJ, et al. the cross national epidemiology of obsessive compulsive disorder. The Cross National Collaborative Group. *J Clin Psychiatry*. 1994;55(Suppl):5-10.
- 7. Karno M, Golding JM, Sorenson SB, Burnam MA. The epidemiology of obsessive-compulsive disorder in five US communities. *Arch Gen Psychiatry*. 1988; 45:1094-1099.
- 8. Greenberg PE, Sisitsky T, Kessler RC, Finkelstein SN, Berndt ER, Davidson JRT, Ballenger JC, Fyer AJ. The economic burden of anxiety disorders in the 1990s. *J Clin Psychiatry*. 1999; 60:427-435.
- 9. Katzelnick DJ, Kobak KA, DeLeire T, Henk HJ, Greist JH, Davidson JRT, Schneier FR, Stein MB, Helstad CP. Impact of generalized social anxiety disorder in managed care. *Am J Psychiatry*. 2001; 158:1999-2007.
- 10. Kessler RC, Andrade LH, Bijl RV, Offord DR, Demler OV, Stein DJ. The effects of co-morbidity on the onset and persistence of generalized anxiety disorder in the ICPE surveys. International Consortium in Psychiatric Epidemiology. *Psychol Med.* 2002; 32:1213-1225
- 11. Markowitz JS, Weissman MM, Ouellette R, Lish JD, Klerman GL. Quality of life in panic disorder. *Arch Gen Psychiatry*. 1989; 46:984-992.

- 12. Rogers MP, White K, Warshaw MG, et al. Prevalence of medical illness in patients with anxiety disorders. *Int J Psychiatry Med.* 1994; 24:83-96.
- 13. Sonne SC, Back SE, Diaz Zuniga C, Randall CL, Brady KT. Gender differences in individuals with comorbid alcohol dependence and post-traumatic stress disorder. *Am J Addict*. 2003; 12:412-423.
- 14. Kessler RC, Foster CL, Saunders WB, Stang PE. Social consequences of psychiatric disorders, I: Educational attainment. *Am J Psychiatry*. 1995; 152:1026-1032.
- 15. Kessler RC, Walters EE, Forthofer MS. The social consequences of psychiatric disorders, III: probability of marital stability. *Am J Psychiatry*. 1998; 155:1092-1096.
- 16. Kessler RC, Berglund PA, Foster CL, Saunders WB, Stang PE, Walters EE. Social consequences of psychiatric disorders, II: Teenage parenthood. *Am 7 Psychiatry*. 1997; 154:1405-1411.
- 17. Costello EJ, Egger HL, Angold A. Development epidemiology of anxiety disorders. In: Ollendick TH, March JS, eds. *Phobic Anxiety Disorders in Children and Adolescents: A Clinician's Guide to Effective Psychosocial and Pharmacological Interventions.* Oxford, UK: Oxford University Press; 2003:pages 61-91.
- 18. Pine DS, Cohen P, Gurley D, Brook J, Ma Y. The risk of early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Arch Gen Psychiatry*. 1998; 55:56-64.
- 19. Kendler KS. Major depression and generalised anxiety disorders. Same genes, (partly) different environments revisited. *Br J Psychiatry Suppl.* 1996; 30:68-75.
- 20. Hettema JM, Neale MC, Kendler KS. A review and meta-analysis of the genetic epidemiology of anxiety disorders. *Am J Psychiatry*. 2001; 158: 1568-1578.
- 21. Safren SA, Gershuny BS, Marzol P, Otto MW, Pollack MH. History of childhood abuse in panic disorder, social phobia, and generalized anxiety disorder. *J Nerv Ment Dis.* 2002; 190:453-456.
- 22. Young EA, Abelson JL, Curtis GC, Nesse RM. Childhood adversity and vulnerability to mood and anxiety disorders. *Depression Anx.* 1997; 5:66-72.

- 23. Nishith P, Mechanic MB, Resick PA. Prior interpersonal trauma: the contributions to current PTSD symptoms in female rape victims. *J Abnorm Psychol.* 2000; 109:20-25.
- 24. Stein MB, Walker JR, Anderson G, et al. Childhood physical and sexual abuse in patients with anxiety disorders and in a community sample. *Am 7 Psychiatry*. 1996; 153:275-277.
- 25. Pine DS, Cohen P, Johnson JG, Brook JS. Adolescent life events as predictors of adult depression. *J Affect Disord*. 2002; 68:49-57.
- 26. Pigott TA. Gender differences in the epidemiology and treatment of anxiety disorders. *7 Clin Psychiatry*. 1999; 60(suppl 18):4-15.
- 27. Turgeon L, Marchand A, Dupuis G. Clinical features in panic disorder with agoraphobia: a comparison of men and women. *J Anxiety Disord.* 1998; 12:539-553.
- 28. Yonkers KA, Bruce SE, Dyck IR, Keller MB. Chronicity, relapse, and illness course of panic disorder, social phobia, and generalized anxiety disorder: findings in men and women from 8 years of follow-up. *Depress Anxiety*. 2003; 17:173-179.
- 29. Breslau N. Gender differences in trauma and posttraumatic stress disorder. *J Gend Specif Med.* 2002; 5:34-40.
- 30. Brady KT. Pharmacotherapeutic treatment for women with PTSD. Program and abstracts of the 154th Annual Meeting of the American Psychiatric Association; May 5-10, 2001; New Orleans, Louisiana. Symposium 12E.
- 31. Castle DJ, Deale A, Marks IM. Gender differences in obsessive compulsive disorder. *Aust N Z J Psychiatry*. 1995; 29:114-117.
- 32. Zoellner LA, Feeny NC, Cochran B, Pruitt L. Treatment choice for PTSD. *Behav Res Ther*. 2003; 41:879-886.
- 33. Brady K, Pearlstein T, Asnis GM, et al. Efficacy and safety of sertraline treatment of posttraumatic stress disorder. A randomized controlled trial. *JAMA*. 2000; 283:1837-1844.
- 34. Biederman J, Rosenbaum JF, Bolduc-Murphy EA, et al. A 3-year follow-up of children with and without behavioral inhibition. *J Am Acad Child Adolesc Psychiatry*. 1993; 32:814-821.
- Kagan J, Snidman N. Early childhood predictors of adult anxiety disorders. *Biol Psychiatry*. 1999; 46: 1536-1541.

- 36. Schwartz CE, Snidman N, Kagan J. Adolescent social anxiety as an outcome of inhibited temperament in childhood. *J Am Acad Child Adolesc Psychiatry*. 1999; 38:1008–1015.
- 37. Kagan J, Snidman N, Arcus D, Reznick JS. In: *Galen's Prophecy: Temperament in Human Nature*. Boulder, CO: Westview Press; 1997.
- 38. Rasmussen SA, Eisen JL. Epidemiology of obsessive compulsive disorder. *J Clin Psychiatry*. 1990; 51(suppl):10-13.
- 39. Cjte S, Tremblay RE, Nagin D, Zoccolillo M, Vitaro F. The development of impulsivity, fearfulness, and helpfulness during childhood: patterns of consistency and change in the trajectories of boys and girls. *J Child Psychol Psychiatry*. 2002; 43:609-618.
- 40. Steiner H, Ryst E, Berkowitz J, Gschwendt MA, Koopman C. Boys' and girls' responses to stress: affect and heart rate during speech task. *J Adolesc Health*. 2002; 30(4 suppl 1):14-21.
- 41. Hayward C, Killen JD, Hammer LD, et al. Pubertal stage and panic attack history in sixth- and seventh-grade girls. *Am J Psychiatry*. 1992; 149:1239-1243.
- 42. Reed V, Wittchen HU. DSM-IV panic attacks and panic disorder in a community sample of adolescents and young adults: how specific are panic attacks? *T Psychiatr Res.* 1998; 32:335-345.
- 43. McClure EB, Monk CS, Nelson EE, et al. A developmental examination of gender differences in brain engagement during evaluation of threat. *Biol Psychiatry*. 2004; 55:1047-1055.
- 44. Pearlstein TB, Frank E, Rivera-Tovar A, Thoft JS, Jacobs E, Mieczkowski TA. Prevalence of axis I and axis II disorders in women with late luteal phase dysphoric disorder. *J Affect Disord*. 1990; 20:129-134.
- 45. Cohen LS, Sichel DA, Dimmock JA, et al. Postpartum course in women with preexisting panic disorder. *J Clin Psychiatry*. 1994b; 55:289-292.
- 46. Hertzberg T, Wahlbeck K. The impact of pregnancy and puerperium on panic disorder: a review. *J Psychosom Obstet Gynaecol.* 1999; 20:59-64.
- 47. Cohen LS, Sichel DA, Dimmock JA, et al. Impact of pregnancy on panic disorder: a case series. *J Clin Psychiatry*. 1994a; 55:284-288.
- 48. Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the National Comorbidity Survey I: lifetime prevalence, chronicity and recurrence. *J Affect Disord*. 1993; 29:85-96.

- 49. Weissman MM, Klerman GL. Sex differences and the epidemiology of depression. *Arch Gen Psychiatry*. 1977; 34:98-111.
- Lewinsohn PM, Gotlib IH, Lewinsohn M, Seeley JR, Allen NB. Gender differences in anxiety disorders and anxiety symptoms in adolescents.
 J Abnorm Psychol. 1998; 107:109-117.
- 51. Bailey JW, Cohen LS. Prevalence of mood and anxiety disorders in women who seek treatment for premenstrual syndrome. *J Womens Health Gend Based Med.* 1999; 8:1181-1184.
- 52. Wittchen H-U, Becker E, Lieb R, Krause P. Prevalence, incidence and stability of premenstrual dysphoric disorder in the community. *Psychol Med.* 2002; 32:119-132.
- 53. McLeod DR, Hoehn-Saric R, Foster GV, Hipsley PA. The influence of premenstrual syndrome on ratings of anxiety in women with generalized anxiety disorder. *Acta Psychiatr Scand.* 1993; 88:248-251.
- 54. Cameron OG, Kuttesch D, McPhee K, Curtis GC. Menstrual fluctuation in the symptoms of panic anxiety. *J Affect Disord*. 1988; 15:169-174.
- 55. Williams KE, Koran LM. Obsessive-compulsive disorder in pregnancy, the puerperium, and the premenstruum. *J Clin Psychiatry*. 1997; 58:330-334.
- 56. Chrousos GP, Torpy DJ, Gold PW. Interactions between the hypothalamic-pituitary-adrenal axis and the female reproductive system: clinical implications. *Ann Intern Med.* 1998; 129:229-240.
- 57. Sandman CA, Glynn L, Wadhwa PD, Chicz-DeMet A, Porto M, Garite T. Maternal hypothalamic-pituitary-adrenal dysregulation during the third trimester influences human fetal responses. *Dev Neurosci.* 2003; 25:41-49.
- 58. Phillips N, Dennerstein L, Farish S. Psychological morbidity in obstetric-gynaecology patients: testing the need for expanded psychiatry services in obstetric-gynaecology facilities. *Aust N Z J Psychiatry*. 1996; 30:74-81.
- 59. Levine RE, Oandasan AP, Primeau LA, Berenson AB. Anxiety disorders during pregnancy and postpartum. *Am J Perinatol*. 2003;20:239-248.
- 60. Seng JS, Oakley DJ, Sampselle CM, Killion C, Graham-Bermann S, Liberzon I. Posttraumatic stress disorder and pregnancy complications. *Obstet Gynecol*. 2001;97:17-22.
- 61. Sholomskas DE, Wickamaratne PJ, Dogolo L, O'Brien DW, Leaf PJ, Woods SW. Postpartum onset of panic disorder: a coincidental event? *J Clin Psychiatry*. 1993;54:476-480.

- 62. Wisner KL, Peindle KS, Hanusa BH. Effects of childbearing on the natural history of panic disorder with comorbid mood disorder. *J Affect Disord*. 1996; 41:173-180.
- 63. Maina G, Albert U, Bogetto F, Vaschetto P, Ravizza L. Recent life events and obsessive-compulsive disorder (OCD): the role of pregnancy/delivery. *Psychiatry Res.* 1999; 89:49-58.
- 64. Sichel DA, Cohen LS, Dimmock JA, Rosenbaum JF. Postpartum obsessive compulsive disorder: a case series. *J Clin Psychiatry*. 1993; 54:156-159.
- 65. Creedy DK, Shochet IM, Horsfall J. Childbirth and the development of acute trauma symptoms: incidence and contributing factors. *Birth*. 2000; 27:104-111.
- 66. Wijma K, Soderquist J, Wijma B. Posttraumatic stress disorder after childbirth: a cross sectional study. *J Anxiety Disord*. 1997; 11:587-597.
- 67. Carter CS, Altemus M, Chrousos GP. Neuroendocrine and emotional changes in the postpartum period. *Prog Brain Res.* 2001; 133:241-249.
- 68. Kendrick KM, Keverne EB, Hinton MR, Goode JA. Oxytocin, amino acid and monoamine release in the region of the medial preoptic area and bed nucleus of the stria terminalis of the sheep during parturition and suckling. *Brain Res.* 1992; 569:199-209.
- 69. Altemus M, Redwine LS, Leong YM, Frye CA, Porges SW, Carter CS. Responses to laboratory psychosocial stress in postpartum women. *Psychosom Med.* 2001; 63:814-821.
- 70. Altemus M, Deuster PA, Galliven E, Carter CS, Gold PW. Suppression of hypothalamic-pituitary-adrenal axis responses to stress in lactating women. *7 Clin Endocrinol Metab.* 1995; 80:2954-2959.
- 71. Heck H, de Castro JM. The caloric demand of lactation does not alter spontaneous meal patterns, nutrient intakes, or moods of women. *Physiol Behav.* 1993; 54:641-648.
- 72. Mezzacappa ES, Guethlein W, Vaz N, Bagiella E. A preliminary study of breast-feeding and maternal symptomatology. *Ann Behav Med.* 2000;22:71-79.
- 73. Virden SF. The relationship between infant feeding method and maternal role adjustment. J Nurse Midwifery. 1988;33:31-35.
- 74. Freeman EW, Sammel MD, Liu L, Martin P. Psychometric properties of a menopausal symptom list. *Menopause*. 2003;10:258-265



Anxiety Disorders Association of America 8730 Georgia Avenue, Suite 600 Silver Spring, MD 20910, USA www.adaa.org