Anxiety Disorders and Gender

Dan J. Stein
Bavi Vythilingum
Editors

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Foreword

Large epidemiologic studies have consistently found the anxiety disorder to be one of the most common psychiatric disorders in the world. Anxiety disorders have a negative impact on physical and mental health as well as on educational, social, and occupational functioning and overall quality of life. It has long been known that anxiety disorders are much more prevalent in women than men, but more recent work has also found differences in comorbidity, symptoms, and how these disorders affect each gender. As the term "sex" refers to biological aspects and "gender" refers to the psychological and social aspects of maleness or femaleness, it is appropriate to discuss these differences in anxiety disorders as "gender differences," to acknowledge the biological and psychosocial components that are inherent in their etiology and persistence. What is not yet known is if there are gender differences in the psychobiology or treatment responses of the anxiety disorders and if these are found to exist, what clinical implications they may have.

This book, edited by two international authors on anxiety disorders (Dan Stein and Bavi Vythilingum), is a treasure trove of the collective wisdom of the leading anxiety disorder psychiatrists and psychologists from across the globe. Each chapter addresses the gender aspects of one of the anxiety and related disorders: general anxiety, panic, social anxiety, obsessive-compulsive and related disorders, trauma, and stress-related disorders. There are also summary chapters on anxiety disorders in women and men.

Genetics, neuroimaging, gonadal hormones, psychological diagnostic tests, clinical evaluation, pharmacology, and psychotherapy of each disorder are elegantly discussed. The essential role of cognitive behavioral therapy is emphasized, with modifications for specific diagnoses. Gender differences in phenomenology are illustrated, for example, women with obsessions are more likely to focus on contamination and cleaning, while men are more likely to focus on sexual and symmetry obsessions. Interestingly, these differences appear to be stable across cultures, suggesting that biological or cross-cultural gender roles may play a role. Gender differences are also illustrated for body dysmorphic disorder in which women are more likely to focus on facial and breast details, while men are more likely to be preoccupied by inadequate musculature. In terms of comorbidity by gender, women with obsessive-compulsive disorders are more likely to suffer from depression, while men are more likely to have a substance abuse disorder.

The importance of disorders in the perinatal period, including those – the majority – that are persistent disorders from earlier onset, and their implications for treatment and child development are given due prominence.

These examples and many others contribute to the compelling case for the study of gender differences in psychiatry to better understand and treat mental disorders with increased specificity. The need for gender-specific early intervention is gaining more prominence as the possibilities and implications for both genders become more apparent. The authors have made a critical advance in this work on gender differences in anxiety disorders. This valuable book will not only inform the reader of the most recent knowledge but also greatly assist them in the optimal care of all patients suffering from anxiety disorders.

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Introduction

Anxiety disorders are the most prevalent of the psychiatric disorders, and therefore of particular interest to both the practising clinician and to the mental health policy-maker. In this volume we also often refer to the anxiety and related disorders, as the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* (American Psychiatric Association 2013) has split the older category of anxiety disorders into anxiety disorders, obsessive-compulsive and related disorders, and trauma- and stressor-related disorders. The DSM-5 approach takes into account a growing evidence-base which suggests that there is both diagnostic validity and clinical utility in separating out these conditions, but the manual also lists these disorders directly adjacent to one another in order to emphasize their significant overlap (Stein et al. 2011).

The volume approaches these disorders through the important prisms of sex and gender. There is a growing appreciation in psychiatry and clinical psychology that sex and gender have important implications for diagnosis, for pathogenesis, and for management. Consider, for example, the finding that in countries with lower traditionality of female gender roles there is a narrowing of differences between men and women in prevalence of mental disorders (Seedat et al. 2009). Relatedly, there is also growing awareness of the complexity of sex and gender; these are constructs that entail biological, psychological, and sociocultural mechanisms.

Indeed, part of the interest of the current volume is that chapters necessarily cover a broad range of different disciplines in an effort to unpack sex and gender in relation to anxiety and related disorders. In this brief introduction, we wish to make a few key points about the relevant literature, in the hope that this will provide the reader a conceptual framework for the remainder of the volume. We cover in turn, some key advances at the intersection of sex/gender and the anxiety and related disorders, as well as a number of the important gaps that remain.

Key Advances

Several key advances have been made at the intersection of sex/gender and anxiety related disorders. In the realm of diagnosis and evaluation, both clinical and community studies have repeatedly emphasized important differences in the prevalence and presentation of anxiety and related disorders in women (Baxter et al. 2013).

Community studies demonstrate that anxiety and related disorders are more common in females throughout the world, with the onset of this difference occurring between pregnancy and menopause. At the same time, when it comes to treatment-seeking, the female predominance is not always apparent; social anxiety may for example be more likely to interfere with the professional and social lives of men than of women, accounting for a less skewed distribution of males in social anxiety disorder clinics. DSM-5 has taken particular care to document gender issues in each of its chapters.

A second important advance has been in the awareness that sex and gender-related variables impact on the pathogenesis of mental disorders. As above, such mechanisms may range from the biological to the cultural. Puberty, the menstrual cycle, pregnancy, and the menopause are important precipitants for onset, exacerbation, recurrence and relapse of a number of mental disorders, including several of the anxiety and related disorders. These events certainly involve complex changes in hormonal profiles, and in multiple downstream aspects of neurocircuitry and neurochemistry (McEwen 2014). It is also notable that girls demonstrate more internalizing coping styles and more anxiety than boys; suggesting the importance of developmental factors in contributing to the complex array of factors involved in pathogenesis of anxiety and related disorders (Altemus et al. 2014). At the same time it is important to emphasize that such differences are not absolute and, indeed, the magnitudes of such differences across gender is small.

A third important advance has been in awareness of the impact of sex and gender-related variables on the pharmacotherapy and psychotherapy of mental illness. There is increased understanding, for example, of pharmacodynamic and pharmacokinetic differences between males and females for a range of different medications. Lower doses of z-drugs, for example, may be required in females. Similarly, psychotherapy of anxiety and related disorders may well need to address gender-related issues. For example, in many places in the world, it may be relatively easier for a woman not to have to do exposure work around agoraphobic concerns; clinicians may need to be particularly encouraging of basic psychotherapy principles under such circumstances.

Key Gaps

At the same time that there have been important advances at the intersection of sex/gender and the anxiety and related disorders, it is also important to emphasize multiple gaps in our understanding.

First, despite the attention of community and clinical studies to sex differences in psychopathology, and despite the attention to gender in DSM-5, at the end of the day sex and gender have not impacted on diagnostic criteria for key serious mental disorders, nor for common mental disorders (American Psychiatric Association 2013). That said, perhaps this is not so much a deficit in understanding as a reasonable approach to enhance the diagnostic validity and clinical utility of the nosology. Thus, for example,

while it behoves the clinician to be aware of telescoping of symptoms in women with certain conditions (e.g. gambling disorder), this does not imply that women have such a distinct symptom profile that they warrant a different diagnostic criteria set.

Second, despite significant research in laboratory, clinical, and community settings on sex and gender-related factors in the pathogenesis of anxiety and related disorders, our knowledge base remains fragmentary. Indeed, it should be noted that for many differences between males and females, we remain uncertain whether these reflect biological or psychosocial mechanisms. While there are clearly differences in brain structure across the sexes, the mechanisms and implications behind such differences are far from clear, and reductionistic conclusions should be avoided. There is a definite need for longitudinal studies of sex and gender-related variables in relationship to psychopathology; this may shed great light on differences between males and females in years to come. There is also a need to focus not only on proximal (psychobiological) mechanisms but also on distal (evolutionary) mechanisms; for example, in women factors that promote reproductive success may also contribute to a range of health problems (Jasienska 2013).

Third, despite many advances in the prevention and treatment of anxiety and related disorders, it is remarkable how little is known about what can be done specifically to improve male or female clinical outcomes during the management of anxiety and related disorders. It is again possible that this reflects not so much a lack of knowledge about appropriate pharmacotherapy and psychotherapy of anxiety and related disorders, as the fact that the treatments provided are substantially similarly across gender. This is not to downplay the need and scope for much further development of this important area of investigation

Conclusion

In recent decades there has been growing awareness of sex and gender-related variables in both the basic and clinical context. During this time there has also been growing work on anxiety and related disorders, and a growing number of women have entered the professional workforce of psychiatry and clinical psychology. A volume on the intersection between sex/gender and anxiety-related disorders therefore seems very timely; the prism of sex and gender provides an important perspective on these prevalent and disabling disorders. This volume will cover a broad range of conditions, and will attempt to synthesize the start of the art knowledge in this area. In subsequence chapters leading authorities will address each of the major anxiety disorders, obsessive-compulsive and related disorders, and trauma- and stressor-related disorders.

At the same time, despite important advances it is remarkable that so much remains unknown. In the laboratory context, male rats have been a model organism for many years, and there is a real need to include female rats in experiments (Clayton and Collins 2014). In the clinical context, it is clear that women suffer much more than men from anxiety and related disorders, and while some of the

contributing factors to this phenomenon have been investigated, many others have not. Historically, psychiatry has at times had a patriarchal and condescending approach to women. Going forwards, it must take sex and gender issues with utmost seriousness. We hope that this volume makes one contribution, albeit relatively restricted, to this important goal.

Dan J. Stein and Bavi Vythilingum

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Generalized Anxiety Disorder

Katja Beesdo-Baum and Kevin Hilbert

A 32-year old woman complains of permanent nervousness, irritability and inability to relax. She has been working as a nurse on an oncology unit since she returned from maternity leave with her now 2-year old son. During shifts, she has trouble concentrating on her work because of concerns relating to her son's wellbeing in day care. She has also fears about possible accidents or harm coming to him even when he is with his father or the grandparents. "What if he runs on the street and gets caught by a car? What if they have an accident when driving home from kindergarten?" She therefore checks her mobile phone frequently or calls to hear that everything is o.k. The time she is spending with her family is usually well organized and any special events such as going on a trip are planned with extensive lists in advance. Situations outside of her personal control such as a short-notice business trip of her husband usually lead to intense distress. Just recently, related to adverse experiences of dying patients at work, she also developed excessive worries about severe illnesses befalling her son, herself or her husband which could lead to destruction of her family.

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According to the recently published fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; APA 2013), generalized anxiety disorder (GAD) is characterized by worry and anxiety about a range of events and situations occurring on the majority of days for a minimum of 6 months. Worry and anxiety are excessive, difficult to control and accompanied by several symptoms. These include restlessness, muscle tension, irritability, fatigue and difficulties in concentration or sleep. Among the situations and events worried about are mostly everyday matters such as financial affairs, family or health issues. The current diagnostic criteria have undergone no significant change from DSM-IV (APA 2000). Although the 11th Version of the *International Classification of Diseases* (ICD-11)[1] will possibly be more similar to GAD criteria in DSM-5 than the currently still employed ICD-10 (WHO 1993), it will likely still consider a broader symptom list (including gastrointestinal and autonomic arousal symptoms) and will not emphasize uncontrollability of anxiety and worry.

Epidemiology

Prevalence and Age of Onset

Generalized anxiety disorder is a common disorder in the general population with lifetime prevalence estimates ranging between 1.7 and 5 %, 12-month prevalence estimates being only slightly lower between 1.2 and 4.6 %; the point prevalence is 1–2 % (Lieb et al. 2005; Wittchen et al. 2011; Kessler et al. 2012; Beesdo et al. 2009b). The lifetime morbid risk as of age 75 has been estimated to be 9 % (Kessler et al. 2012). In primary medical care, GAD has a high point prevalence of about 4–8 % (Wittchen 2002; Munk-Jorgenson et al. 2006; Kroenke et al. 2007), accounting for about 8–9 % of all cases of mental disorders in this setting (Lieb et al. 2005; Wittchen 2002). Both in the general population and in primary medical care, females are overall approximately 1.5–2 times as likely as males to meet criteria for GAD, although the female preponderance for GAD may not emerge before mid-adolescence (Copeland et al. 2014) and increases with age (Beesdo-Baum and Knappe 2012). Lastly, GAD is very prevalent in specialist mental health care settings, with point prevalence rates over 10.0 % (Brown and Barlow 2002; Bobes et al. 2011).

The first onset of GAD may occur at any time from childhood to late adulthood. Compared to other anxiety disorders, the median age of onset in community-based samples is at 30 years relatively late (Kessler et al. 2012). The incidence sharply increases in adolescence (Burstein et al. 2013; Copeland et al. 2014; Beesdo et al. 2010b) after which new cases steadily emerge until old age (Kessler et al. 2012). An early onset, however, has been linked to a more severe progression of the disorder (Rubio and Lopez-Ibor 2007). Gender effects on the age of onset are not definite.

[1] http://apps.who.int/classifications/icd11/browse/f/en#/http%3a%2f%2fid.who.int%2ficd%2fentity%2f1712535455. Entered on March 25, 2014.

While there is some evidence for a slightly earlier age of onset in women (Steiner et al. 2005; Beesdo et al. 2009b) and the female preponderance in GAD diagnoses appears to arise at a very early age (Parker and Hadzi-Pavlovic 2004; Burstein et al. 2013; Beesdo-Baum and Knappe 2012), other studies did not report gender differences (e.g. Goncalves and Byrne 2012; McLean et al. 2011).

Course

The natural course of GAD in community samples can be described as waxing and waning (Wittchen et al. 2000; Angst et al. 2009; Beesdo 2006) and occurring in recurring episodes of several months or years (Kessler et al. 2005a; Burstein et al. 2013; Grant et al. 2005), with symptom-free intervals in about half of the cases (Angst et al. 2009). Nevertheless, individuals with GAD are affected by the condition in about 50–60 % of the years between first onset and last episode (Kessler et al. 2005a). Persistence is similar among those with shorter and longer episode durations indicating high recurrence among those with short episode durations. Even among adults with GAD indicating a maximum episode duration of only 6–11 months, episodes re-occurred in about 6.5 years; those with longer maximum episodes were affected within 10.4 years (Kessler et al. 2005a). The mean time in episode since first disorder onset in affected adolescents was 65 months (Burstein et al. 2013). A prolonged and chronic course of GAD occurs in clinical samples. In an 8-year naturalistic follow-up study of patients with GAD, spontaneous remissions may occur (men 56 %, women 46 %) but are mostly not persisting (relapses in 43 % of men and 36 % of women) (Yonkers et al. 2003). In primary care patients with GAD, the cumulative probability of full or partial recovery within 2 years was 39 and 54 %, respectively; roughly half of the fully remitted cases experienced a partial or full recurrence of symptoms (Rodriguez et al. 2006). There are no consistent indications that sex differences in course patterns of GAD symptomatology are significant either in clinical or primary care (Rodriguez et al. 2006; Yonkers et al. 2003) or in community samples (Angst et al. 2009). Of note, among those with a GAD diagnosis, syndromatic shifts are often observed suggesting that full diagnostic remission is rare on the long run (Angst et al. 2009; Rubio and Lopez-Ibor 2007; Beesdo 2006).

Comorbidity

As for virtually all other mental disorders, comorbidity is not unusual for GAD. Even in community samples, about 90 % of individuals with GAD are also affected by at least one other mental disorder either at the same time or at any other time during the life course (Kessler et al. 2002a, 2005b; Hoyer et al. 2002; Carter et al. 2001; Copeland et al. 2014). Conversely, GAD is often a comorbid condition in other mental disorders (de Graaf et al. 2003; Faravelli et al. 2004; Copeland et al. 2014). Overall, strongest associations are generally found for mood disorders as well as for

other anxiety disorders (particularly social anxiety disorder and panic disorder as well as separation anxiety disorder), while associations with substance use disorders and impulse-control disorders as well as childhood externalizing or behaviour disorders are lower and less consistent (e.g. Carter et al. 2001; Grant et al. 2005; Lee et al. 2009; Burstein et al. 2013; Copeland et al. 2014; Kessler et al. 2005a). In addition, some studies indicate associations with dependent and avoidant personality disorders as well as with somatoform disorders and pain conditions (Faravelli et al. 2004; Beesdo et al. 2009a, 2010a). Eating disorders (anorexia and bulimia nervosa) have been rarely examined in general population samples but there are also some indications that these disorders co-occur more frequently than expected by chance in individuals with GAD (Faravelli et al. 2004; Carter et al. 2001; Beesdo 2006). Studies on gender differences in comorbidity patterns are rare; yet the association between GAD and mood disorders appears to be particularly pronounced in females (Beesdo 2006).

Regarding the temporal order of onset, GAD may occur prior to, simultaneous or after the onset of any comorbid condition (Kessler et al. 2002a). With regard to any comorbid anxiety disorder (particularly specific phobia and social anxiety disorder), GAD is usually the secondary onset condition; however, GAD also significantly predicts the secondary onset of other anxiety disorders (Lee et al. 2009; Beesdo et al. 2010b). Mood disorders emerge often in the same year as GAD (in about 50 % of comorbid cases) (Kessler et al. 2002a), which challenges differential diagnosis (see below). Substance use disorders mostly occur secondary to the onset of GAD (Kessler et al. 2002a) and risk for secondary substance use disorders is particularly high in individuals with more prolonged GAD episodes (Lee et al. 2009), indicating that alcohol, nicotine or medications may be used to cope with chronic anxiety and worry.

Besides comorbid psychiatric disorders, somatic complaints such as chest pain, irritable bowel and chronic fatigue syndrome as well as medical illnesses (diabetes, hypertension, gastrointestinal and heart diseases) are associated with GAD (Sareen et al. 2005; Lieb et al. 2005). Generally, the presence of comorbid mental or physical disorders confers a greater level of disability in patients with GAD (Sareen et al. 2005).

Personal and Societal Costs

GAD is associated with significant personal burden for the patient as well as costs for the health care system and the society (Andlin-Sobocki and Wittchen 2005; Hoffman et al. 2008). Community studies show, for example, that up to one third of individuals suffering from GAD, even in the absence of depression, report days in the past month on which normal daily activities were limited or impossible to perform due to disorder symptoms; the average number of disability or sick days among these individuals ranged between 1.5 and 5.6 days (Kessler et al. 2002b). Of note, these impairments in role functioning were comparable to those observed in individuals affected by major depression. Similar findings emerged in primary

care studies (Wittchen et al. 2002). Such role impairments considerably reduce subjective health (Schonfeld et al. 1997), quality of life and general wellbeing in GAD patients (Bobes et al. 2011; Beesdo et al. 2009a; Stein and Heimberg 2004) and are mostly intensified if comorbid conditions are present (Beesdo et al. 2009a; Hoffman et al. 2008). Of note, childhood/adolescent GAD was recently shown to have a predictive role for adverse health, financial/educational and social functioning in young adulthood (Copeland et al. 2014). Few studies have investigated the effects of gender on personal burden of GAD, but no differences in quality of life between genders due to diagnosis have been detected so far (e.g. Bobes et al. 2011).

GAD also invokes considerable economic burden, not only because of direct health care costs associated with increased health care utilization and treatment (Berger et al. 2009b; Lieb et al. 2005; Wittchen et al. 2002; Greenberg et al. 1999), but also due to the indirect costs associated with role impairments at work (sick leaves, decreased productivity, early retirement etc.) (Greenberg et al. 1999; Andlin-Sobocki and Wittchen 2005; Hoffman et al. 2008; Gustavsson et al. 2011). In a recent study investigating health care cost per case due to mental disorders in Europe, the costs of GAD per case were higher as compared to other impairing anxiety disorders (obsessive-compulsive disorder, agoraphobia) and higher than the cost per case for major depression (Gustavsson et al. 2011). While treatment seeking seems to be lower in men than in women (see below), no studies have compared the consequences of these different amounts of treatment seeking between genders on health care costs or other markers of economic burden.

Psychobiology

Aetiology and Risk Factors of Generalized Anxiety Disorder

A number of different risk factors have been proposed for GAD, including genetics, personality, attachment style, stressful life events and dysfunctional coping styles. However, empirical evidence is not conclusive for all of these factors and is often incomplete or inconsistent. Additionally, some of the proposed risk factors seem to lack specificity and should rather be regarded as vulnerability for anxiety and anxiety disorders in general (Beesdo et al. 2009b). Here, we will focus on a selection of those factors that have been investigated most extensively.

The specific genetic basis of GAD is not well elucidated. Generally, twin studies revealed heritability estimates of 20–50 % (Giddens et al. 2011; Hettema et al. 2001, 2006; Kendler et al. 2011). This genetic basis of the disorder seems to be largely shared with personality traits such as neuroticism (Hettema et al. 2006) and with a range of other anxiety and mood disorders, which suggests that high comorbidity between these conditions can be partly attributed to genetic factors as well (Cerda et al. 2010). As a consequence, many of the candidate genes proposed for the development of GAD are also somewhat non-specific and associated with other mental disorders as well. This includes polymorphisms in the serotonin-transporter gene (5-HTTLPR; You et al. 2005), the brain-derived neurotrophic

factor (BDNF; Meng et al. 2011) gene, the monoamine oxidase A (MAO-A; Samochowiec et al. 2004; Tadic et al. 2003) gene and in the promoter region of the neuropeptide Y gene that hypothetically reduced resilience to high stress conditions and thereby increased vulnerability and prevalence for subsequent GAD diagnoses (Amstadter et al. 2010). Additionally, an association between a range of anxiety disorders including GAD and genes related to the circadian cycle has been reported (Sipila et al. 2010). The tryptophan hydroxylase (TPH) gene has been frequently investigated as candidate gene for GAD as well, but no differences between patients and healthy controls were found so far (Fehr et al. 2001; You et al. 2005). Given the differences in GAD prevalence between genders, a biological basis for these findings has been proposed (Altemus 2006), including possible genetic differences as well. However, population-based studies found no gender-specific effects in heritability or in the overall genetic basis of the disorder (Hettema et al. 2005). This is true for most candidate gene studies as well, with the notable exception of the MAO-A gene polymorphisms that were found to be relatively gender-specific, being related only or much stronger in women (Samochowiec et al. 2004; Tadic et al. 2003).

Regarding personality traits, research on risk factors for developing GAD has identified three factors, including partly overlapping constructs. Patients generally seem to be more often in a negative affective state and to experience these states for a longer period of time. As such, GAD is moderately associated with negative temperament and neuroticism and negatively correlated with positive temperament (Brown and Naragon-Gainey 2013; Gamez et al. 2007). Secondly, GAD is associated with a pattern of fear of the unknown or unfamiliar, and with interpretation of such situations as threatening and frequently resulting behaviours of avoiding such situations (Carleton 2012), including constructs such as harm avoidance (Rettew et al. 2006; Beesdo et al. 2010b), behavioural inhibition (Maack et al. 2012; Beesdo et al. 2010b) or intolerance of uncertainty (Read et al. 2013). But as these potential risk factors are mostly shared between a wide range of anxiety and other mental disorders, the specificity for GAD is not always clear. For instance, there is some evidence suggesting behavioural inhibition as being relatively specific for the disorder (Maack et al. 2012), while the opposite seems to be the case for intolerance of uncertainty (Boswell et al. 2013). Lastly, GAD seems to be related to increased attempts but reduced subjective success in attempting to control one's own life and emotion. In particular, GAD is negatively associated with perceived control over conditions of life, stressful events and emotional states (Brown and Naragon-Gainey 2013); however, increased inhibition of emotional processing in stressful situations actually increases worry severity (Price and Mohlman 2007). Research on gender differences in GAD related personality traits is sparse, but suggests that there are some differences between the sexes regarding personality traits, with women often scoring higher on negative affectivity and trait anxiety, and also seeming to be more intolerant of uncertainty while at the same time experiencing subjectively less control about life and events surrounding them (McLean and Anderson 2009). However, there are still relatively few data on gender differences in personality traits that are possibly of relevance to GAD (McLean and Anderson 2009).

There is a clear relationship between anxiety disorders in general and GAD in particular, and attachment style. Insecure or poor childhood attachment styles have been linked to GAD (Cassidy et al. 2009; Marganska et al. 2013). Additionally, the relationship between childhood attachment styles and future GAD symptoms seems to be mediated by inadequate emotion regulation strategies and competences (Marganska et al. 2013). First studies also pointed towards an interaction between attachment styles and gender, with the relationship between perceived attachment quality towards fathers and GAD symptoms being stronger in males than in females (van Eijck et al. 2012), while GAD patients in general reported more maternal rejection and role reversal than healthy persons (Cassidy et al. 2009). On a broader scale of parental or family risk factors, individuals with GAD also reported more childhood maltreatment (Moffitt et al. 2007); yet parental overprotection appears also to be a risk factor for the development of disorder (Beesdo et al. 2010b).

As with a wide range of mental disorders, stressful life events have been related to the development of GAD. For GAD, such events include separation events during childhood (Beesdo et al. 2010b), stress due to high psychological job demands during adulthood (Melchior et al. 2007) and events related to loss and danger over the whole course of the lifetime (Kendler et al. 2003). As a subset of all potentially stressful life events, trauma events have been related to GAD as well (Roemer et al. 1996), including past physical or sexual abuse (Safren et al. 2002), although such events are not specific for GAD. They do, however, increase the probability of additional comorbid anxiety disorders or depression (Safren et al. 2002). In addition to being connected to the onset of GAD, stressful life events also increase the risk of relapse in already GAD-diagnosed patients (Francis et al. 2012). Relapse probability here is mainly linked to the number of stressful events in the last 4 weeks. Additionally, some types of events seemed to be particularly symptom-inducing, including events related to health, death and family friends or household (Francis et al. 2012). So far, no influence of gender on the sensitivity to stressful life events has been reported (Kendler et al. 2003).

Specific coping styles, especially related to coping with aversive emotional arousal, also mark an important risk factor of GAD. Generally, in GAD patients, awareness of one's own emotions seems to be less than usual and more dysfunctional strategies of emotion regulation are used (Roemer et al. 2009). In the long term, the use of these dysfunctional strategies predicts a diagnosis of GAD (Tull et al. 2009). Many such inefficient strategies have been identified so far, among them self-blaming, catastrophizing and rumination (Legerstee et al. 2011) and clinically well-known dysfunctional strategies such as reassurance seeking (Cougle et al. 2012) and cognitive avoidance (Olatunji et al. 2010). The specificity of such maladaptive behaviour for GAD is somewhat less well investigated; however, rumination in particular seems to be characteristic for GAD compared to other anxiety disorders (Legerstee et al. 2011), although probably less specific when compared to depressive disorders. Matching these findings, worry and rumination have been found to mediate the association between cognitive avoidance and anxiety, with this mediating effect being attributed as one of the factors establishing the high

coherence between GAD and major depression (Dickson et al. 2012). Conversely, reassurance seeking has been shown to be an additional factor yielding possibly high specificity for GAD in comparison to depressive disorders (Cougle et al. 2012). However, reassurance seeking seems to be less specific when compared to other anxiety disorders (Cougle et al. 2012). Generally, most of the discussed dysfunctional emotion regulation strategies aim at inhibiting or avoiding processing of especially aversive emotions, while acceptance of emotions is less prevalent in these individuals (Roemer et al. 2009) and a negative association between emotion acceptance and processing and GAD symptom severity has been demonstrated (Price and Mohlman 2007). Besides a decreased disposition or willingness to endure negative emotional states, other variables may also influence these maladaptive coping styles: for example, some studies found a heightened level of emotions in GAD (Mennin et al. 2007, 2009).

Possible gender differences in dysfunctional emotion regulation strategies are currently still in question as findings are few and inconsistent. Some studies did not find any gender differences in the use of these strategies (e.g. Legerstee et al. 2011; Olatunji et al. 2010); while others conclude that some strategies such as cognitive avoidance or negative problem orientation (Robichaud et al. 2003) or even most such strategies are used more frequently by women than by men (Nolen-Hoeksema 2012). Additionally, there is preliminary data suggesting that men may actually benefit from some strategies usually classified as dysfunctional, especially emotion inhibition, while women in fact suffer from such strategies (Bardeen et al. 2013). Potentially, this finding that usually dysfunctional strategies of emotional regulation do not yield the same negative impact in men as in women might be a first hint on why GAD is more prevalent in females.

Psychological Models of Generalized Anxiety Disorder

Besides findings of selected risk factors and variables contributing to GAD, there are also some more elaborated psychological models of the disorder integrating different etiological and/or pathogenic aspects. Here, we will outline three of the more popular of these models: the Avoidance Model of Worry and GAD (Borkovec 1994, 2004), the Emotion Dysregulation Model (Mennin et al. 2002) and the Intolerance of Uncertainty Model (Dugas et al. 1998).

The central idea behind the Avoidance Model of Worry and GAD is that worry is a dysfunctional emotion regulation strategy that actually inhibits autonomic and somatic arousal and dampens aversive emotional states. Additionally, worry serves as a strategy to avoid exposure to topics that are even more important and more aversive (Borkovec and Roemer 1995). Possibly, the mechanism behind this dampening effect is a shift from anxiety-related autonomic system activating mental images to less activating, and more cognitively mediated, verbal thoughts about the problem (Behar et al. 2005; Borkovec and Inz 1990). Due to the large exclusion of the somatic and affective parts of fear and the concentration on cognitive processing, worry likewise seems to inhibit successful exposure to aversive emotions

including further processes such as habituation to feared stimuli and situations and extinction of maladaptive fear-stimulus connections (Stapinski et al. 2010). Given the initial decrease in negative affect and autonomic arousal, worry gets reinforced and is more likely to be used again in the future. From this perspective, worry is actually a strategy to avoid profoundly dealing with one's own emotions, giving the model its name. Additionally, many GAD patients believe worry to be actually helpful for avoiding negative consequences and therefore successful problem solving, which again increases the likelihood of worry being used again as emotion regulation strategy in the future (Behar et al. 2009). More recent further developments of the model suggest that individuals with GAD may be hypersensitive to boosts of negative emotions and therefore use worry to maintain a steady state of negative emotions that prevents increased changes in emotion in response to negative events (Llera and Newman 2014).

The idea of experienced hyperarousal when facing negative emotional states is also relevant for the Emotion Dysregulation Model. Here, a disposition to experience negative emotions earlier, faster and stronger than other people is enhanced by decreased abilities to access, identify or understand emotions in general, but also one's options to regulate one's own emotions (Mennin et al. 2005; McLaughlin et al. 2007; Salters-Pedneault et al. 2006). As patients also hold mainly negative beliefs about experiencing any emotion, they quickly attempt to minimize or control these negative affects, resulting in mostly dysfunctional emotion regulation or emotion expression strategies, including worrying (Behar et al. 2009). However, over time, dysfunctional regulation strategies may again increase the likelihood of negative emotions occurring (Mennin et al. 2005).

Worry as a dysfunctional strategy of emotion regulation is also present in the Intolerance of Uncertainty Model of GAD. Here, especially uncertain or ambiguous situations are interpreted as threatening, since these situations allow for the chance of negative consequences to occur. These consequences are considered unacceptable without regard to their actual likelihood (Carleton 2012). In attempting to cope with these aversive expectations, GAD patients again use worry as a strategy for emotion regulation or for preventing the feared consequence to occur at all (Behar et al. 2009). However, in the Uncertainty Model of GAD, worry leads to feelings of anxiety on an affective level, and poor problem orientation and cognitive avoidance on a cognitive and behavioural level (Dugas et al. 1998). Again, cognitive avoidance aims at reducing autonomic arousal coming from anxiety and worry, and together with poor problem orientation in turn affects future behaviour in uncertain situations and future worry.

(Neuro-)Biological Models of Generalized Anxiety Disorder

Research on the biological underpinnings of GAD is relatively sparse compared to other anxiety and mental disorders. Still, early reliable findings have emerged in the literature, especially regarding structural and functional alterations found in GAD patients. In comparison, even fewer hormonal and molecular findings are available

so far, although these may prove equally fruitful for expanding our knowledge on GAD aetiology.

On the level of brain areas involved in attentional control, emotional processing, cognitive avoidance and similar functions tied to the disorder, research up to now has focused on a relatively small group of structures, including the amygdala, anterior cingulate gyrus (ACC) and prefrontal cortex (PFC); the latter one especially in its dorsolateral and ventrolateral parts (Hilbert et al. 2014). Among these, the amygdala has been shown to exhibit increased volume (Etkin et al. 2009) and abnormal responding during tasks of attention, emotional perception and processing, or anticipation in GAD (Etkin and Schatzberg 2011; McClure et al. 2007; Nitschke et al. 2009). Additionally, the amygdala is supposedly related to the mediation and enhancement of autonomic hyperarousal (Macefield 2009). Therefore, amygdala abnormalities have been related particularly to the clinical symptoms of apprehensive expectations, feeling on edge or muscle tensions. PFC and ACC, on the other hand, are related to the processing, evaluation and (re-)appraisal of emotions, with especially the ventral parts of the PFC being closely tied to negative feelings. While structural findings are sparse in these regions, functional data on the prefrontal cortex indicated hyperactivation in GAD patients (Price et al. 2011; Strawn et al. 2012), while ACC findings are mixed (Etkin and Schatzberg 2011; McClure et al. 2007). Clinically, these findings have been related to excessive worries, difficulties in stopping worrying and maladaptive cognitive control strategies as cognitive avoidance. However, activation of both PFC and ACC have also been implicated in successful emotional processing, giving rise to the question of why these patterns of neural responding are unsuccessful in GAD patients. While a definite answer to this question has not yet been found, mounting evidence points towards additional perturbations on the level of brain circuitry. Supposedly indicating regulatory and inhibitory processes, there is structural and functional connectivity between the amygdala and the PFC and ACC in healthy persons, and this has been repeatedly found to be significantly decreased in GAD (Etkin et al. 2009; Etkin and Schatzberg 2011; Tromp et al. 2012). Possibly, this indicates failure to recruit both structures in an efficient way and marks the shift from functional cognitive strategies of emotion regulation to the dysfunctional set of strategies subsumed under worrying.

While some of these findings seemed to emerge consistently during recent years, many other results are still mixed and can only be interpreted with caution, even in these comparatively well-investigated regions. Generally, relatively few studies investigated neurofunctional and neurostructural alterations in GAD, using a relatively broad accumulation of methods, paradigms and samples. This results in only a few replications being available (especially compared to affective disorders as depression), and many findings should be regarded as preliminary. Additionally, structures such as the amygdala or ACC have been implicated in a wide range of anxiety and other mental disorders (e.g. Shin and Liberzon 2010), and with the current literature mostly lacking studies employing a comparative design including GAD and at least one other disorder group, the specificity of the above findings is still in question. Further, most neuroimaging studies investigating GAD so far have

used moderately to highly comorbid samples, often including subjects with other anxiety disorders or depression.

There is also some knowledge available on pathophysiological changes in hormone and neurotransmitter functioning in GAD, although the number of related studies is relatively limited. So far, these abnormalities seem to be most closely tied to serotonin, GABA and cortisol (e.g. Connor and Davidson 1998). For serotonin, reduced levels of the neurotransmitter probably due to increased reuptake have been reported (Brewerton et al. 1995). Reuptake might be chronically increased due to permanent stress (Tafet et al. 2001), and these abnormal serotonin levels have been related to the affective changes observed in GAD and accounting for a certain overlap with major depression. For GABA, being one of the most important inhibitory neurotransmitters, the functioning of the corresponding receptor sites may be reduced, as studies on the very similar benzodiazepine receptors have suggested (Connor and Davidson 1998). Possibly, this reduced GABAergic sensitivity is connected to the sympathetic hyperarousal observed in GAD, as it leads to the vagal system being not as efficient in inhibiting sympathetic arousal as in healthy controls (Thayer and Lane 2000). Data on cortisol is very mixed so far, with both increased and decreased cortisol levels being reported, allowing for no clear interpretation of the abnormalities found so far. As a working hypothesis to merge these conflicting results, an initial cortisol secretion increase followed by long-term decrease due to chronicity was proposed (Steudte et al. 2011). However, further data to support this promising notion are awaited. Most studies did not investigate gender differences for the hormones and neurotransmitters discussed here. When investigated (as for serotonin), no gender differences were detected (Hernandez et al. 2002; Park et al. 2010).

Diagnosis

Generalized anxiety disorder can be diagnosed according to the criteria outlined in the recently published *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5; APA 2013) and the *International Classification of Diseases*, 10th edition (ICD-10; WHO 1993). Diagnoses are best made based on structured or standardized clinical interviews. These interviews usually allow for both classifications to be applied in the diagnostic process, considering that the DSM-IV/DSM-5 and the ICD-10 only partially overlap in diagnostic criteria specified for GAD: While both classifications name anxiety, worry and apprehension as the cardinal features of GAD, and as being present over at least 6 months, only the DSM-5 states that worry and anxiety must be excessive and difficult to control. Additionally, both systems require a number of further symptoms with DSM-5 focusing on symptoms of tension and hypervigilance (3 out of 6; 1 in children) while the ICD-10 requires 4 symptoms out of a broader symptom list that also includes autonomic arousal, gastrointestinal and other general and unspecific symptoms. A further major difference between classifications concerns clinically significant distress or impairment, which is only required in the DSM-5. In conclusion, the DSM-5 focuses more on

the psychological symptoms of anxiety, whereas the ICD-10 focuses more on the physiological symptoms of anxiety (Hoyer and Beesdo 2006). It is expected that ICD-11 will adopt some of the DSM-5 criteria (excessiveness, distress/impairment) so that definition of GAD will be more similar in both classification systems than is currently the case.

During the preparation of the DSM-5, it was proposed that the criterion on difficulty in control worrying be exchanged with a list of specified behavioural symptoms such as behavioural avoidance, safety behaviours or reassurance seeking (Andrews et al. 2009), and that this would make the diagnostic criteria for GAD more similar to other anxiety disorders that all include behavioural criteria, specifically avoidance. Recent research has shown that GAD patients use behavioural strategies in attempting to control their worries and that these behaviours are of clinical importance, as they can be used to predict the long-term outcome of psychotherapy (Beesdo-Baum et al. 2012a). However, the proposed changes were not implemented in the current edition of the DSM due to lack of further empirical data, particularly with regard to external validators (Starcevic et al. 2012). Nevertheless, these symptoms may be clinically useful in diagnosis and treatment of patients with GAD.

Differential Diagnosis

Differential diagnosis in GAD may be difficult but is of great importance, as the overlap of GAD with other mental disorder groups such as anxiety, mood or somatoform disorders is considerable and significantly aggravates the diagnostic process (Bener et al. 2013). Overall, there are five major domains that should be carefully evaluated during differential diagnosis: other anxiety disorders, particularly social anxiety disorder, obsessive-compulsive disorders, depressive disorders, somatic symptom and related disorders, particularly somatic symptom disorder and illness anxiety disorder, and somatic diseases. Somatic diseases, symptoms or the influence of other injuries, substances or medical conditions may cause physiological symptoms similar to those found in GAD, and may also cause subsequent worry and anxiety as well as rather unspecific symptoms such as sleep disturbances. To determine whether such symptoms should be attributed to somatic or physiological causes, a careful medical history and examination is warranted. If worries and anxiety are mostly related to health topics, but no or only minor somatic abnormalities have been detected, differential diagnosis should also feature illness anxiety disorder. Here, health topics are usually the only focus of anxiety or worrying, while in GAD other worry topics are present as well (APA 2013). Anxiety, worrying and rumination are also main features of social anxiety disorder and depressive disorder. However, in social anxiety disorder, anxiety and worries should mainly occur when experiencing or anticipating social situations in which evaluation by others is likely or possible, while anxiety and worry in GAD should be present regardless of social evaluation and mostly include not only worry topics that are related to social situations (APA 2013). Differentiating GAD and major depression is more difficult, as

both disorders do not only share frequent worrying or rumination, but also many accompanying physiological symptoms such as problems sleeping or concentrating (Hoyer and Beesdo-Baum 2011). However, rumination in major depression mostly focuses on past events and frequently features depressive notions of loss, failure and guilt; worry in GAD, in contrast, mostly focuses on future events and features more anxious ideas of danger or risk. Ascertaining past periods with only anxiety and worry but no depressed mood may also justify a separate diagnosis of GAD in patients presenting with symptoms of both anxiety and depression. Lastly, frequently re-occurring thoughts and images eliciting anxiety and worry are also present in obsessive-compulsive disorder, but are experienced as intrusive and unreasonable. Additionally, they tend to comprise a range of topics typically found in obsessive-compulsive disorder, such as infection, tidiness or violent or sexual images (Hoyer and Beesdo-Baum 2011).

Clinical Interviews for Diagnosis

There is a wide range of clinical interviews available for the diagnosis of generalized anxiety disorder, ranging from structured to fully standardized ones. These interviews are all based on the DSM-IV diagnostic criteria, but as no major changes occurred for GAD during the transition to the DSM-5, they are still applicable for DSM-5 GAD. Internationally, the most commonly used interviews are the Composite International Diagnostic Interview (CIDI; Robins et al. 1988; Kessler and Ustun 2004; WHO 1990), the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First et al. 1997), the Mini-International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al. 1998) and the Anxiety Disorders Interview Schedule for DSM-IV (ADIS-C/P; Albano and Silverman 1996). Among these, the CIDI is the only fully standardized clinical interview, while all others of the above are structured interviews, giving both the interviewer and the patient more degrees of freedom during the assessment, however, also requiring clinically trained personnel to successfully administer the interview. Besides GAD, all of the above interviews can also be used to diagnose a range of other mental disorders, for example for differential diagnosis or assessment of comorbidity. Here, the CIDI and SCID are the most comprehensive interviews allowing for the broadest range of mental disorder; however, common comorbid diagnoses such as major depression or substance abuse and dependence are available in all of the above interviews. Regarding the available timeframe, the CIDI is the only interview allowing for a lifetime diagnosis of GAD, while all of the other interviews only address current episodes of the disorder. For the ADIS, however, there is a lifetime version available (ADIS-IV-L; Di Nardo et al. 1994). On the other hand, the CIDI is also the interview with the longest duration, while the MINI is usually the shortest.

There are also diagnostic interviews available for diagnosing GAD in children and adolescents, with the most prominent being the Kiddie Schedule for Affective Disorders – Present and Lifetime Version (K-SADS-PL; Kaufman et al. 1997). The K-SADS-PL is a semi-structured interview and suitable for children and adolescents

between 6 and 18 years of age. Like its adult counterparts, the K-SADS-PL covers a range of mental disorders, including GAD and its most common comorbidities, and allows for the diagnosis of current episodes and lifetimes diagnoses. Besides information provided by the child or adolescents itself, information provided by the parents and if available by school and other sources is considered.

Recognition in Primary Medical Care

Although GAD is a prevalent anxiety disorder and GAD patients are high utilizers of general health care resources, recognition rates are surprisingly low (Lieb et al. 2005; Wittchen et al. 2002). When confronted with a patient presenting GAD symptoms, only about two-thirds of all general practitioners recognized the presence of a mental disorder at all, and only one-third recognized GAD as the specific diagnosis (Munk-Jorgenson et al. 2006; Wittchen et al. 2002). Recognition is generally better when patients report anxiety among the reasons for consulting the general practitioner. However, it seems that GAD patients also struggle to identify their problems as they mainly describe physiological and unspecific psychological symptoms such as pain or difficulties sleeping (Allgulander 2012; Wittchen et al. 2002). Consequently, the number of patients seeking treatment in settings specialized on mental disorders is relatively low, especially when compared to patients consulting their general practitioner (Wittchen et al. 2002).

The presence of comorbid disorders has been found to both facilitate and aggravate the help-seeking and recognition of GAD (Bener et al. 2013; Vesga-Lopez et al. 2008; Wittchen et al. 2002, 2012). Empirically, studies so far have demonstrated that comorbid depression makes case recognition easier, possibly as it exacerbates GAD symptom severity (Bener et al. 2013) but does also increase diagnosis recognition significantly (Wittchen et al. 2002). Gender was not found to have a significant influence on recognition (Bystritsky et al. 2012; Munk-Jorgenson et al. 2006; Wittchen et al. 2002), although males were found to seek help – or more specifically treatment – less frequently than females (Vesga-Lopez et al. 2008; Manassis et al. 2004). Possibly, lower treatment seeking in men is one factor accounting for different prevalence estimates for GAD in men and women in primary care settings.

Evaluation

Standard measures for GAD symptom severity are typically self-report-questionnaires. Despite having been relevant for many aspects in the diagnostic process, for example, for supporting diagnosis or measuring progress during therapy, such measures are likely to gain further importance due to the DSM-5's emphasis on dimensional evaluation of disorders. During the development of DSM-5, a set of brief self-rating dimensional anxiety scales was developed for each of the anxiety

diagnoses including GAD. Good psychometric properties and classification performance were demonstrated for these scales in clinical and non-clinical studies (LeBeau et al. 2012; Beesdo-Baum et al. 2012b; Knappe et al. 2013, 2014), so that the scales are now available for researchers and clinicians for further use at www.psychiatry.org/dsm5.

Beyond these novel scales, there is a range of other, more traditional self-rated measures for GAD symptomatology, of which only the most widely used will be presented here, namely the Penn State Worry Questionnaire (PSWQ; Meyer et al. 1990), the Generalized Anxiety Disorder 7 (Spitzer et al. 2006), the Generalized Anxiety Questionnaire-IV (GAD-Q-IV; Newman et al. 2002), the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith 1983) and the Screen for Child Anxiety Related Emotional Disorders Scale (SCARED; Birmaher et al. 1997). While the PSWQ, GAD-7 and GAD-Q-IV are specifically relevant for GAD, with the GAD-7 and the GAD-Q-IV screening for the current presence of the DSM-IV/DSM-5 criteria and the PSWQ focusing on the intensity, severity and subjective controllability of worry, both the HADS and SCARED cover a broader spectrum of mental disorders, including questions related to other anxiety disorders (for both HADS and SCARED) and depression (only for HADS). As a pure measure for symptom severity, the PSWQ is probably the most widely used instrument. For all of these questionnaires, reasonable to good psychometric properties have been reported, including good specificity and sensitivity (Birmaher et al. 1997; Bjelland et al. 2002; Brown et al. 1992; Newman et al. 2002; Spitzer et al. 2006; Kroenke et al. 2007).

The most widely used clinician-rated severity measure for GAD is the Hamilton Anxiety Rating Scale (Hamilton 1959) for which a structured interview guide is also available (GADSS; Shear et al. 2001). However, more novel clinician-based instruments consistent with the DSM criteria are available such as the Generalized Anxiety Disorder Severity Scale (GADSS; Shear et al. 2006) and the DSM-IV GAD severity scale (DGSS; Stein 2013). The latter assesses both symptom severity and symptom frequency.

Developmental Aspects

When diagnosing generalized anxiety disorder in children and adolescents, a careful evaluation of presenting symptoms is warranted, as verifying the diagnostic criteria of GAD in these patients often proves even more difficult than in adult GAD. In fact, the development of more sensitive diagnostic instruments and criteria has been identified as one of the major tasks for improving GAD recognition in children and adolescents (Beesdo et al. 2009b). The DSM-5 only specifies one difference in criteria for GAD in children versus adults: Only 1 and not 3 associated symptoms are required in children (APA, 2013). This developmental difference in GAD criteria has found empirical support (Burstein et al. 2013; Beesdo-Baum et al. 2011); yet there are further indications for a more developmentally sensitive diagnosis. Specifically, children may experience shorter but more frequent episodes (Beesdo

2006; Burstein et al. 2013). Children may also find it hard to reflect and report on distress and impairment so that a more flexible handling of this criterion or additional diagnostic information from other sources such as parents, close friends or teachers is advisable (Beesdo-Baum et al. 2011). Moreover, restlessness and muscle tension are relatively rare among affected children or young adolescents, while poor concentration and irritability are more common symptoms (Burstein et al. 2013; Beesdo 2006). Particularly in children it may advantageous to evaluate any anxiety or worry-related behaviours such as excessive reassurance seeking from caregivers or teachers (Andrews et al. 2010).

Geriatric Aspects

As in children and adolescents, diagnosing generalized anxiety disorder can be challenging in older adults. While some of these difficulties can be related to diagnostic criteria, there are also specific factors impacting the sensitivity and reliability of the diagnosis in the elderly, including a decreased willingness to provide information about symptoms of mental disorders and frequent combination and overlap of somatic and psychological symptoms (as reviewed in Kogan et al. 2000). Especially with regard to the latter point, it is again of high importance to use sufficiently sensitive and reliable diagnostic instruments for disorder recognition. However, as the current generation of interviews and scales has been developed mainly for use in adult populations, the psychometric properties of these instruments in older populations are often unclear and sometimes even questionable (for a review, see Alwahhabi 2003). However, there are some initial studies that have systematically investigated the use of self-report measures in the elderly. So far, these studies cautiously recommend the use of either the HADS or the PSWQ for use in older adults (Alwahhabi 2003; Hopko et al. 2000; Wetherell et al. 2007). Additionally, the use of multiple methods, possibly including also laboratory and physical examinations and other sources for information such as close relatives, has been recommended (Kogan et al. 2000).

Pharmacotherapy

Pharmacological treatment is the most common type of treatment in patients with GAD (Wittchen et al. 2002). Overall, about 60 % of recognized GAD patients in primary care are treated by their general practitioner, while only 20 % of patients are referred to specialized care (psychotherapist, psychiatrist). Unfortunately, overall treatment rates are considerably lower due to lack of recognition or failure to provide treatment despite diagnosis of the disorder (Wittchen et al. 2002). In a large community sample, only 14 % of all GAD cases reported to have seen a psychiatrist in the past year, where the proportion of cases receiving minimally adequate treatment is higher (51 %) than in the general medical care section (20 %) (Wang et al. 2005). While females were found to have overall higher rates for any treatment

utilization than males, they were less likely to receive mental health specialty treatment (Wang et al. 2005). Among primary care patients slightly more affected women than men use psychotropic medication (61 % compared to 54 %; Berger et al. 2009a). Comorbidity with depression was shown to increase the probability for receiving pharmacotherapy (Wittchen et al. 2002). When prescribing these drugs, possible gender differences in efficacy and side effects should always be considered, as the pharmacokinetics and pharmacodynamics may differ between men and women (Keers and Aitchison 2010).

Overall, a wide range of psychotropic drugs is available for GAD treatment (Baldwin et al. 2014), with the modern antidepressants being the first-line treatment choice, given the overall chronic-persistent nature of GAD and the respectively required long-term treatment. Selective serotonin reuptake inhibitors (SSRIs) as well as serotonin and noradrenaline reuptake inhibitors (SNRIs) have established efficacy (Baldwin et al. 2005, 2011). Commonly used SSIR that are licensed in many countries for GAD are paroxetine and escitalopram; common SNRIs are venlafaxine and duloxetine. Generally, both SSRIs and SNRIs anxiolytic efficacy is supported by a reasonable number of studies, and both SSRIs and SNRIs are usually tolerated well (Baldwin et al. 2005). The SSRI sertraline has also been reported as appropriate for children and adolescents (Rickels and Rynn 2001) (Walkup et al. 2008). As all these drugs are commonly used to treat depression, there may be an additional positive effect of this therapy in the frequent cases of comorbid GAD and depression (Durham 2004). Generally, there is little research on possible gender differences regarding efficacy or side effects for these drugs, although it was suggested that the female hormonal cycle might interact with serotonergic antidepressants (Martenyi et al. 2001). Some sparse research on gender-specific effects is available for specific serotonergic drugs: While men and women responded equally to sertraline, treatment response seems to be lower for women treated with fluoxetine but higher for women treated with venlafaxine (Pollack et al. 2003; Simon et al. 2006; Steiner et al. 2005). Additionally, according to Allgulander 2012), sertraline and fluoxetine are first choice treatments during pregnancy, while paroxetine has been reported as unsafe during pregnancy (Marks et al. 2008).

Besides SSRIs and SNRIs, tricyclic antidepressants (TCAs) are commonly used for GAD treatment. Here, efficacy is supported by studies as well, but side effects are more disruptive and more common (Baldwin et al. 2005). Therefore, the current recommendation regarding TCAs is to use these drugs only when SSRIs and SNRIs have not led to a sufficient improvement for the patient and other alternatives have been tested or are not available (Baldwin et al. 2014). As with SSRIs and SNRIs, patients with comorbid GAD and depression may also benefit from the antidepressant effect of the drug. However, TCAs should not be used in severe depression when there is a risk of suicide, as an overdose is considered highly toxic (Baldwin et al. 2014). While there are no studies investigating possible interactions between TCA medication and gender, studies on depression suggested interactions between the female hormonal cycle and TCA efficacy and tolerability, but again the possible implication for clinical practice have not been fully investigated (Hildebrandt et al. 2003; Kornstein et al. 2000).

For short-term treatment and rapid symptomatic relief in GAD, mostly benzodiazepines and also buspirone have been used. Both features established short-term efficacy, although buspirone seems to be somewhat less effective (Chessick et al. 2006). Both are usually well tolerated (Berger et al. 2011; Chessick et al. 2006). However, benzodiazepines pose a risk of dependency which is usually related to duration of drug intake (Baldwin et al. 2005; Durham 2004). No such risk is present for buspirone (Baldwin et al. 2005). However, buspirone has been reported to show dysphoric side effects (Durham 2004) and thus should not be used when comorbid depression is present. All in all, both benzodiazepines and buspirone should mainly be used for acute treatment, and possible adverse effects should be monitored closely, while long-term use of benzodiazepines should be avoided (Durham 2004).

There is also a wide range of other drugs that have been used for GAD, including anticonvulsants, antipsychotics or plant-based drugs. However, for most of these possible alternatives, few data are available regarding response and tolerability, including possibly severe side effects. Therefore, these drugs should be avoided if possible and first- or second-line treatments as outlined above should be used. If these fail to achieve the intended effect and one of these alternatives is prescribed, possible side effects should be monitored very closely.

One notable exception is pregabalin, an anticonvulsant recently available for GAD treatment (Allgulander 2012; Baldwin et al. 2011). Here, efficacy and tolerability have been demonstrated for GAD (Montgomery et al. 2008; Stein et al. 2008) and there may be an antidepressive effect as well (Stein et al. 2008). Until now, no study has reported gender differences in efficacy or tolerability for pregabalin.

Psychotherapy

In a large community sample, 17 % of the GAD cases reported to have seen a psychologist or other nonpsychiatrist mental health professional, including social worker or counselor in a mental health setting, or used a mental health hotline in the past year, with almost two thirds receiving minimally adequate treatment (Wang et al. 2005).

Psychotherapy, particularly cognitive-behavioural therapy (CBT), has proven efficacy in the treatment of GAD with large effect sizes (Mitte 2005; Hunot et al. 2007; Cuijpers et al. 2014). Improvements generally remain stable at follow-up and positive effects also occur on co-occurring symptoms such as depression (Cuijpers et al. 2014). However, given heterogeneity between study findings and the fact that on average only half of the treated patients fully remit from GAD through treatment, further research is necessary regarding both advancing disorder models and improving active treatment ingredients. Most studies have tested the effects of treatments containing multiple CBT intervention components such as applied relaxation, self-control desensitization, self-monitoring of worrying, stimulus control, cognitive restructuring and various forms of anxiety management (Hoyer and Gloster 2009). More complex CBT programmes, however, are not necessarily beneficial over narrower treatments such as pure behavioural therapy (Cuijpers et al. 2014), suggesting that identification of active treatment ingredients is essential.

Individual interventions with proven efficacy as stand-alone treatments are applied relaxation (Öst 1987) and massed worry exposure (Hoyer et al. 2009). Applied relaxation is a coping technique. Patients learn how to relax based on progressive muscle relaxation and to decrease the time to relaxation using several practice steps. Finally, they will be able to apply a short relaxation procedure whenever first signs of anxiety, worry or tension arise in order to reduce autonomic arousal and cope with the anxiety eliciting situations. Massed worry exposure attempts to target more directly the putative underlying core pathogenic mechanisms of the disorder (Hoyer and Beesdo-Baum 2012). Patients are exposed to emotions and cognitions that are avoided during episodes of worrying. For that purpose, an image script is generated for the most feared worry outcomes (e.g. "My son and husband die in a car accident") and patients are confronted with this image until anxiety reactions decrease. More research is necessary on the effectiveness of specific interventions and possible add on components contributing to more favourable treatment outcomes. For example, there are indications that greater emphasis on interventions targeting dysfunctional GAD behaviours such as reassurance, avoidance and safety behaviours might be beneficial (Beesdo-Baum et al. 2012a). Very favourable effect sizes in more recently developed alternative treatment approaches employing mindfulness and acceptance based techniques (Roemer et al. 2008) can also be interpreted in this way. Further, more research is necessary regarding potential incremental beneficial effects of combined psychotherapy and pharmacotherapy as initial findings are inconsistent (Walkup et al. 2008; Crits-Christoph et al. 2011). Finally, considerably more work is needed regarding more personalized or tailored treatment based on patient characteristics. There are to date only few and inconsistent findings regarding predictors for treatment outcome in patients with GAD (Hoyer and Gloster 2009) suggesting heterogeneity in terms of best treatment choice. With few exceptions where females appear to have worse treatment outcomes than males (Manassis et al. 2004), gender does mostly not emerge as significant predictor (e.g. Payne et al. 2011).

Conclusion

Although gender differences have been consistently revealed for GAD in terms of prevalence, with women being more commonly affected than men, the causes for this difference remain largely unknown. Researchers have not consequently conducted separate analyses for males and females or explored the moderating or predictor role of gender. Given this background, focused re-analyses of available data and well-planned novel studies are necessary to unravel the causes of gender differences in GAD.

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Panic Disorder

Borwin Bandelow and Katharina Domschke

Epidemiology

Like other anxiety disorders, panic disorder (PD) is more frequent in women than in men. In European prevalence studies, the female-to-male ratio was 2.5 for panic disorder and 3.1 for agoraphobia (Wittchen et al. 2011). In the US National Comorbidity Survey, the gender ratio was 1.8 for both panic disorder and agoraphobia. Men and women showed a similar age of onset of PD in one study (Barzega et al. 2001). In another study, men reported an earlier age of onset and a shorter duration of illness, while the clinical presentation was similar for both genders (Clayton et al. 2006). In a comparison of PD in women and men, it was found that the rate of agoraphobia was higher in women than in men and the course was more chronic, as evidenced by an increase in the recurrence of panic symptoms following remission (Yonkers et al. 1998).

Panic disorder is highly comorbid with other mental disorders, potentially in a gender-specific fashion. Women were reported to have higher rates of comorbid depression, dependent or histrionic personality disorders, and bulimia nervosa than men, while lower rates of cyclothymia, body dysmorphic disorder, depersonalization disorder, alcohol or substance abuse, and borderline and schizoid personality disorders were observed (Clayton et al. 2006; Barzega et al. 2001; Andrade et al. 1996).

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Diagnosis and Evaluation

Patients with panic disorder experience recurrent unexpected panic attacks, are persistently worried about having more panic attacks, or change their behavior in maladaptive ways because of the panic attacks. According to the DSM-5 criteria (APA 2013), panic attacks are abrupt surges of intense fear or discomfort that reach a peak within minutes, accompanied by at least 4 of 13 defined physical and cognitive symptoms. Panic attacks may occur for no apparent reason or in expected situations. In around two thirds of the cases, the individuals with panic disorder develop agoraphobia, which is the fear of two or more of the following situations: using public transportation; being in open spaces or enclosed places; standing in line or being in a crowd; or being outside of the home alone. The individuals fear these situations because of thoughts that escaping might be difficult or embarrassing when panic symptoms occur.

Specific panic scales have been developed for assessing severity of panic disorder and agoraphobia and for measuring treatment success. The Panic and Agoraphobia Scale (PAS; Bandelow 1999) and the Panic Disorder Severity Scale (Shear et al. 1997) do not only measure panic attack severity but also agoraphobic avoidance behavior, anticipatory anxiety, worries about health, and restrictions in quality of life.

Psychobiology

Psychosocial and neurobiological causes may contribute to the higher prevalence of panic disorder in women.

Psychosocial Factors

One possible explanation for a female-dominant susceptibility to anxiety disorders is that women have more reason to be anxious due to their lower physical strength. However, anxiety disorders are often characterized by unrealistic fears of harmless objects or situations, such as the fear of elevators, mice, or shopping malls, and not by fears that represent a real threat (e.g., being assaulted). Specific phobias have an evolutionary background (e.g., only individuals with an inborn fear of spiders, snakes, and other dangerous animals survived) instead of being a consequence of negative conditioning experiences (like having been bitten by a spider). Likewise, agoraphobia usually does not occur after experiences like being trapped in an elevator or being hurt in a mass panic. Therefore, it is difficult to explain the higher frequency of panic disorder and agoraphobia by a higher occurrence of dangerous situations in women.

Women are significantly affected by chronic stressors, such as domestic conflicts, a double role as homemaker and worker, lower wages, or lower promotion prospects (Belle and Doucet 2003). However, traumatic life events occur more frequently in men: The US National Comorbidity Survey found that 51.2 % of women and 60.7 % of men reported exposure to at least one traumatic event (Kessler et al. 1995).

Although there is no evidence from twin studies for gender differences in the underlying structure of environmental risk factors for anxiety disorders (Hettema et al. 2005), one single study observed that life events played a significant role in precipitating PD onset, specifically in women, with a particular impact of life events related to interpersonal conflict or health-related issues (Barzega et al. 2001). As women are more often subject to sexual abuse (Kessler et al. 1995), this could explain the higher prevalence rate in females. In a retrospective study, it was found that childhood sexual abuse was reported more often in adult patients with PD than in healthy controls (Bandelow et al. 2002). However, over 90 % of panic patients in this study did not report forced sexual acts during their childhood. Moreover, there should be some caution to interpret the association of sexual abuse and panic disorder in a retrospective study as a direct causal relationship without considering possible mediator variables. Future studies are warranted to further elucidate possible gender-specific effects of life events on the development of PD (see Klauke et al. 2010 for a review).

Differences in the Expression of Fears

Could gender differences in anxiety disorders simply represent an underreporting of symptoms by males? Corresponding to their social role of being brave and fearless, men may feel more uncomfortable than women fully disclosing their distress for fear of being viewed as vulnerable or weak. Some data did not support gender differences in "courage," but found differences in cognitive domains, e.g., in "anxiety sensitivity" (Schmidt and Koselka 2000). Anxiety sensitivity, a cognitive risk factor for panic psychopathology and an intermediate phenotype of pathological anxiety, refers to fears of anxiety-related sensations particularly pertaining to physical concerns (McNally 2002). Apart from genetic factors (see below), differences in anxiety sensitivity have been explained by socialization processes that encourage fearfulness in girls (Stewart et al. 1997).

If gender specificity was mainly a cultural phenomenon, it could be expected that the female-to-male ratio would be different in different cultures. However, PD was found to be relatively consistent, with a few exceptions, in rates and patterns across different countries and there are no major differences between different cultures regarding the female-to-male ratio (Weissman et al. 1997).

Evolutionary Perspectives

From an evolutionary perspective, fearless men may have had a survival benefit, as they were more successful in killing wild animals for nourishing themselves and their families and defending their territory and food resources against intruders (McDonald et al. 2012). Most aggressive acts are committed by males, as reflected by the fact that only 13 % of jail inmates are women (Minton 2013). On the other hand, women who were more anxious about their children may have been more successful in guaranteeing the survival of their offspring during the evolution of humankind. On the other hand, data testing evolutionary hypotheses have indicated that gender roles are surprisingly variable across time and space.

Neurobiological Factors

Several neurobiological mechanisms that may possibly be involved in the etiology of PD have been investigated with regard to their gender specificity. Elucidating the biological substrate of gender-specific susceptibility to panic disorder may help to better understand the etiology of anxiety disorders in general.

Serotonin

As most drugs used for the treatment of PD influence serotonergic neurotransmission, and alterations of the serotonin system have been found in panic patients relative to healthy controls, serotonin (5-HT) seems to be one of the most important neurotransmitters in the pathophysiology of PD (Bandelow et al. 2014). In general, women and men show differences in serotonin brain concentration, baseline serotonin production, and metabolism and availability of serotonin transporter (SERT) (Sramek and Cutler 2011). For example, in a positron emission tomography (PET) study, lower brain regional 5-HT synthesis was found in women (Sakai et al. 2006).

Some studies have investigated gender differences in serotonin systems in patients with PD. In a SPECT study, reduced SERT binding was found in different brain regions, including the raphe nuclei in mainly female patients with current but not remitted PD (Maron et al. 2004a). In a study measuring 5-HT_{1A} receptor binding using PET and the radioligand [carbonyl-^{11}C]WAY-100635, women did not differ from men (Stein et al. 2008). A study employing an improved design using positron emission tomography (PET) and ^{11}C-MADAM did not provide evidence for differential serotonin transporter binding in female patients vs. controls, but identified higher SERT nondisplaceable binding potential in several brain regions, including cortical and raphe areas, and lower SERT binding potential in the hippocampus in males with PD as compared with healthy males (Maron et al. 2011). This result was replicated in a study using PET and the SERT-selective radioligand ^{11}C-DASB, showing increased SERT binding potential in males with PD relative to male controls in the anterior cingulate cortex and midbrain, while no difference was discerned in the female sample (Cannon et al. 2013).

Beta-Adrenergic Sensitivity

An early study observed significant gender differences between patients with PD and controls in electrodermal activity and epinephrine levels before stress exposure (Braune et al. 1994). In a study on potential gender differences in beta-adrenergic receptor sensitivity potentially contributing to the pathophysiology of PD, beta-adrenergic receptor sensitivity was found in female but not in male patients (Kim et al. 2004).

Dopamine

In a female-only sample of patients with PD, striatal DAT binding was evaluated using single-photon emission computed tomography and the ^{123}I-nor-beta-CIT tracer. Significantly higher DAT binding in the striatum was detected in remitted PD females as compared with both currently ill PD and control females (Maron et al. 2010).

Altogether, findings on gender differences in serotonin, adrenergic, and dopamine neurotransmitter systems are sparse, and it is therefore difficult to deduce any conclusions on the etiology and treatment of panic disorder in women from these results.

Hypothalamic-Pituitary-Adrenal (HPA) Axis

Alterations of the hypothalamic-pituitary-adrenal (HPA) axis have been reported in panic patients, with, however, controversial findings. A few studies looked for gender differences in HPA axis activity. In a trial investigating urinary cortisol excretion before and after a randomized, controlled trial (paroxetine vs. placebo/exercise/relaxation) in patients with PD, females showed a significantly higher variability of cortisol excretion compared to males at pre- and post-assessments (Wedekind et al. 2008). When assessing salivary cortisol levels following a 35 % CO_2 challenge (see below) in PD patients compared to healthy volunteers as a measurement of HPA axis activity, higher cortisol values were found in male PD patients (van Duinen et al. 2004). A pilot study exploring gender differences in the relationships between HPA axis alterations and the panic-agoraphobic spectrum (Panic Agoraphobic Spectrum-Self Report lifetime version; PAS-SR) in healthy subjects reported positive correlations of the total PAS-SR score and the panic-like symptoms domain scores with the dehydroepiandrosterone-sulfate (DHEA-S)/cortisol ratio in women only (Dell'Osso et al. 2012).

Carbon Dioxide (CO_2) Hypersensitivity

Patients with PD are hypersensitive to carbon dioxide inhalation (Battaglia et al. 2008). According to Klein's false suffocation alarm theory (Klein 1993), PD may be due to a dysfunctional suffocation alarm monitor misfiring an evolved suffocation alarm system because panic patients are abnormally sensitive to CO_2. A study differentially investigating sensitivity to CO_2 challenge in female patients with PD depending on the menstrual phase reported significantly stronger panic reactions in the early follicular phase than in the midluteal phase (Perna et al. 1995). Also, inhalation of CO_2-enriched air elicited more panic symptoms in healthy women than in male probands (Kelly et al. 2006; Nillni et al. 2010).

Cholecystokinin (CCK) Sensitivity

Another well-established panicogenic test is a challenge with an agonist at the central subtype of the cholecystokinin receptor CCK-4 that produces panic attacks in up to 100 % of patients with PD and, depending on the dose, in up to 50 % of healthy subjects (see Bradwejn and Koszycki 2001; Zwanzger et al. 2012). A study investigating the modulatory role of the serotonin precursor l-5-hydroxytryptophan (5-HTP) on response to a CCK-4 challenge in healthy probands revealed that in females 5-HTP lowered panic attack rates and related cognitive symptoms, while in males only somatic symptoms of panic were alleviated, suggesting a gender-dependent protective effect of 5-HTP in CCK-4 induced panic (Maron et al. 2004b). Also, a 3-day pretreatment with medroxyprogesterone acetate (MP) prior to injection with the CCK-4 analog pentagastrin decreased panic response in women with

PD (Le Melledo et al. 2001), while in a sample of healthy male probands pretreatment with the progestational hormone megestrol showed no significant effect on panic responses to CCK-4 challenge, but did reduce baseline ACTH and cortisol levels, as well as ACTH and cortisol levels after administration of CCK-4 (Raedler et al. 2006). Pre-challenge treatment of male patients with PD and male controls with ethinyl estradiol did not reduce panic response to pentagastrin challenge, but attenuated the challenge-associated increase in heart rate (McManus et al. 2001).

Altogether, the findings regarding CO_2 and CCK hypersensitivity suggest a contribution of female reproductive hormones (below).

Structural/Functional Neuroimaging

To date, only a few neuroimaging studies in PD have paid particular attention to potential gender-specific effects (for comprehensive review, see Dresler et al. 2013). In one structural imaging study using optimized voxel-based morphometry (VBM), a significant volume reduction in the dorsolateral and ventrolateral prefrontal cortices, thalamus, and parietal cortex was identified in females only. Furthermore, volume reduction in the right superior temporal gyrus was found to be greater in females, while reduction in the right amygdala and the bilateral insular cortex was significantly greater in male patients (Asami et al. 2009).

Functional neuroimaging studies have found significantly stronger activation in the amygdala, and increased connectivity of the amygdala, prefrontal, temporal, occipital cortical areas, the basal ganglia and the thalamus in women compared to men during the processing of facial expressions of negative (angry, fearful) emotions (Ohrmann et al. 2010).

Hormonal Factors

Female reproductive hormone-related events (i.e., menstrual cycle and postpartum period) can influence the course of PD (Pigott 1999; Le Melledo and Baker 2004). In animal models, female rats consistently showed greater increases in corticosterone and ACTH in response to acute and chronic stressors. These differences have generally been attributed to the activational effects of gonadal steroids on elements of the HPA axis in females (Young et al. 2001). In humans, estrogen and progesterone may influence mood by interacting with serotonin and norepinephrine neurotransmitter systems implicated in the treatment and pathophysiology of mood and anxiety disorders. Estrogen influences serotonin transporter sites, synthesis, receptor sensitivity, and metabolism of serotonin and decreases monoamine oxidase (MAO) activity (Chakravorty and Halbreich 1997; Seeman 1997; Halbreich 1997). It also enhances noradrenergic neurotransmission by influencing norepinephrine synthesis, responsiveness of the α_2-adrenergic receptor, and metabolism of norepinephrine (Etgen and Karkanias 1994; Schmidt et al. 1997; Halbreich 1997). Estrogen treatment may effectively treat (Gregoire et al. 1996), or prevent the recurrence (Sichel et al. 1995) of postpartum depression. Progesterone may have anxiolytic and sedative properties, mediated by benzodiazepine-like action at the GABA

receptor binding site (Paul and Purdy 1992), but may also lead to dysphoric and mood-destabilizing effects (Pigott 1999; Buckwalter et al. 1999).

Pregnancy

A number of retrospective studies and case series have shown improvement of PD during pregnancy in the majority of women (Cowley and Roy-Byrne 1989; Villeponteaux et al. 1992; Klein et al. 1994; Northcott and Stein 1994; Meshberg-Cohen and Svikis 2007; Guler et al. 2008), although in some studies women continued to experience panic attacks or even had worsening of panic disorder during pregnancy (Cohen et al. 1994a, 1996; Wisner et al. 1996; Verburg et al. 1994; Griez et al. 1995; Dannon et al. 2006). In a larger study, we also found fewer panic manifestations during pregnancy (Bandelow et al. 2006). Moreover, in another large study, pregnant women were less likely to have PD than nonpregnant women (Meshberg-Cohen and Svikis 2007). During the postpartum period, a deterioration of panic symptomatology has consistently been found (Cowley and Roy-Byrne 1989; Sholomskas et al. 1993; Northcott and Stein 1994; Cohen et al. 1994b, 1996; Bandelow et al. 2006).

The changes of panic manifestations during pregnancy and after childbirth may be explained by hormonal changes. During pregnancy, progesterone and estradiol concentrations rise to a maximum at term, when they are several hundred times higher than during the nonpregnancy period (Martin and Hoffman 1986). Around 4–5 days after delivery, there is a precipitate drop in hormone concentrations (Harris et al. 1994). This coincides with the peak symptoms of "maternity blues," potentially induced by a consecutive increase in monoamine oxidase (MAO) activity (cf. Sacher et al. 2010). Accordingly, we found an accumulation of new panic manifestations in the first 5 days after childbirth. In addition, women who had never been pregnant were found to have more panic manifestations than those who had had previous pregnancies (Bandelow et al. 2006; Meshberg-Cohen and Svikis 2007). In female rats, estrogen has been shown to attenuate postpartum-induced anxiety-like behaviors (Furuta et al. 2013), further underlining the notion that the observed increase of anxiety after childbirth may be a consequence of hormonal changes.

Premenstrual Syndrome

Premenstrual dysphoric disorder (PMDD) is an extreme variant of premenstrual syndrome (PMS) and is characterized by a number of psychological symptoms, including depressed mood, anxiety, fatigue, irritability, affective lability, food cravings, sleep disturbances, and physical symptoms (e.g., headache). An exacerbation of preexisting depressive and anxiety disorders has been observed during the premenstrual phase.

PMS is responsive to anxiolytic drugs (e.g., SSRIs; Steiner et al. 2008). Patients with PMDD or PMS, like patients with PD, showed higher sensitivity to laboratory panic provocation challenges (CO_2 or lactate) and higher skin conductance responses to anxiety-provoking stimuli, suggesting that both conditions may share a pathophysiological link (Vickers and McNally 2004; Perna et al. 1995; Facchinetti et al. 1992).

The premenstrual phase is characterized by a high level of progesterone, a moderate level of estrogen, and a gradual rise in follicle stimulating hormone (FSH). At

the end of the premenstrual phase, progesterone and estrogen levels decline rapidly. Although no relationship between progesterone level and premenstrual symptoms has been found (Nillni et al. 2011), it is possible that the rapid decrease in progesterone at the end of the premenstrual phase may be associated with an increase in anxiety vulnerability.

The influence of progesterone on mood and anxiety in the premenstrual phase has also been explained by a periodic opioidergic deficit (Facchinetti et al. 1998) or modulation of γ-aminobutyric acid ($GABA_A$) receptors, which are involved in the control of anxiety, by allopregnanolone, a neuroactive metabolite of progesterone (Nillni et al. 2011).

Among postmenopausal women, panic attacks are relatively common and appear to be an independent risk factor for cardiovascular morbidity and mortality (Smoller et al. 2007). A placebo-controlled study investigating estrogen replacement therapy found no improvements in mood or anxiety symptoms in nondepressive, hysterectomized, postmenopausal women (Demetrio et al. 2011). It has been suggested that progesterone derivatives such as allopregnanolone and other female hormones may play a future role in developing agents for the treatment of anxiety disorders (Le Melledo and Baker 2004).

Altogether, there is a clear association between changes in female reproductive hormones and anxiety manifestations in patients with panic disorder.

Genetic Factors

In first-degree relatives of patients with PD, an up to threefold increased prevalence of the disorder was observed, which indicates significant familiality (Maier et al. 1993; Nocon et al. 2008). Twin studies have proposed a considerable contribution of genetic factors to the pathogenesis of PD, with heritability estimates ranging from 30 to 48 % for PD and over 50 % for agoraphobia (Hettema et al. 2001; Kessler et al. 2005). For "anxiety sensitivity," a risk factor for PD, considerable heritability (37–48 %) has been reported in females only (Jang et al. 1999), although not all studies are consistent (van Beek and Griez 2003).

Segregation analyses have failed to identify a Mendelian mode of inheritance, and this points to a complex genetic inheritance with an interaction of multiple "risk genes," each having only a minor individual influence, together with environmental influences (Vieland et al. 1996).

The most robustly identified risk genes of PD to date are the genes coding for the catechol-O-methyltransferase (COMT), the monoamine oxidase A (MAO_A), the serotonin receptor 1A ($5\text{-}HT_{1A}$), the cholecystokinin B (CCK_B) receptor, the adenosine A_{2A} receptor ($ADORA_{2A}$), and the neuropeptide S receptor ($NPSR_1$) (Deckert et al. 1998, 1999; Domschke et al. 2004, 2007, 2011; Hamilton et al. 2002, 2004; Hosing et al. 2004; Kennedy et al. 1999; Reif et al. 2012; Rothe et al. 2006; Samochowiec et al. 2004; Domschke and Deckert 2012). Interestingly, several female-specific genetic associations have been reported, with the most compelling evidence for the functional val158met polymorphism in the catechol-O-methyltransferase (COMT)

gene, which codes for one of the major methylation enzymes metabolizing monoaminergic neurotransmitters including norepinephrine and dopamine (Domschke et al. 2004, 2007; Hamilton et al. 2002; Samochowiec et al. 2004). This gender-specific finding – potentially mediated by a gene–estrogen interaction (Harrison and Tunbridge 2008; Tunbridge et al. 2008) – is mentioned in the section "Gender-related diagnostic issues" in the chapter on PD in the DSM-5 (APA 2013, p. 212): "There is some evidence for sexual dimorphism, with an association between PD and the catechol-O-methyltransferase (COMT) gene in females only." Furthermore, the longer, more active alleles of a functional variable number tandem repeat polymorphism (VNTR) in the monoamine oxidase A (MAO_A) gene have repeatedly been found to be associated with panic disorder specifically in females, which may be due to the fact that the MAO_A gene is located on the X chromosome (Deckert et al. 1999; Maron et al. 2004b, 2005, 2007; Reif et al. 2012; Samochowiec et al. 2004). Furthermore, the risk-increasing effects of variation in the tryptophan hydroxylase 2 (TPH_2) (Maron et al. 2007), the neuropeptide S receptor ($NPSR_1$) (Domschke et al. 2011), the neuropeptide Y_5 receptor (NPY_{Y5}) (Domschke et al. 2008), the glutamate decarboxylase 1 (GAD_1) (Weber et al. 2012), and the hypocretin receptor 2 ($HCRTR_2$) (Annerbrink et al. 2011) genes on PD or CCK-4 induced panic attacks seem to be female-specific. Finally, genes involved in or interacting with sex hormones have been reported to influence the risk for PD in a potentially female-specific fashion, e.g., the gene for the aldo-keto reductase family 1 C_1 ($AKR1_{C1}$), most likely through changes in progesterone and allopregnanolone levels within and outside the brain (Quast et al. 2014), the gene coding for galanin (GAL) involved in hypothalamic-hypophysiotropic signaling, cosecreted with luteinizing hormone-releasing hormone and possibly acting as a mediator of estrogen action (Unschuld et al. 2008, 2010) or the progesterone receptor gene (PROG) (Ho et al. 2004). The role of female reproductive hormones is further supported by the association between anxiety disorders and estrogen ESR1 and ESR2 polymorphisms in older women (Ryan et al. 2011).

A potential male-specific genetic risk factor in the pathogenesis of PD has repeatedly been suggested for the functional insertion-deletion polymorphisms (I/D) in the angiotensin I-converting enzyme (ACE) gene (Bandelow et al. 2010; Bayoglu et al. 2012; Olsson et al. 2004).

Recently, epigenetic mechanisms such as DNA methylation have been proposed to potentially mediate the interaction between genetic and environmental factors. The first epigenetic study in PD suggests a female-specific association of monoamine oxidase A (MAO_A) gene DNA hypomethylation with PD, potentially mediating a detrimental influence of negative life events, while MAO_A hypermethylation – possibly conferred by positive life events – has been hypothesized to increase resilience towards the disorder (Domschke et al. 2012).

Treatment-genetic studies investigating the genetically controlled variation in therapy response reported the 5-HTT, $5\text{-}HT_{1A}$, COMT, and MAO_A genes to influence the response to treatment with selective serotonin reuptake inhibitors (SSRIs) (Perna et al. 2005; Saeki et al. 2009; Yevtushenko et al. 2010) or cognitive-behavioral therapy (Lonsdorf et al. 2010; Reif et al. 2013) in PD. Also, in such studies, some

of these effects were female-specific/-dominant, e.g., for the 5-HTT gene in mediating response to treatment with paroxetine (Perna et al. 2005) or the MAO_A gene in driving response to cognitive-behavioral therapy (Reif et al. 2013).

Pharmacotherapy and Psychotherapy

Current first-line treatments for panic disorder are the selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) (Bandelow et al. 2008).

Psychotropic medications are more likely to be prescribed to women (Pigott 1999). This may simply be an expression of the higher frequency and severity of the treated disorders (depression, anxiety).

There are some issues that have to be taken into account when treating women with panic disorder. Randomized dose finding studies with psychopharmacological drugs usually do not differentiate between men and women, due to the statistical problems arising from multiple testing. Thus, dose recommendations for these drugs do not take gender differences in body weight, volume distribution, or pharmacokinetics into account. In a number of studies examining pharmacokinetic differences in patients taking antidepressants, higher plasma concentrations, greater volume distribution, greater elimination half-time, and other pharmacokinetic changes were found in women (Frackiewicz et al. 2000; Sramek and Cutler 2011).

However, it is not clear whether these differences affect treatment outcome. In one study, there was a modest trend for women with PD to show superior efficacy at the end of acute sertraline treatment (Clayton et al. 2006). In depression trials, most studies did not find significant differences in treatment response between men and women (Young et al. 2009; Kornstein et al. 2000, 2010).

Among psychological therapies, cognitive-behavioral therapy (CBT) is the most comprehensively studied method for treatment of panic disorder, according to multiple randomized controlled studies (Bandelow et al. 2008). There are no controlled studies showing that gender can moderate outcome of psychotherapy or suggesting specific therapeutic strategies for women with panic disorder.

Conclusion

It is most likely that higher anxiety susceptibility in women is due to a delicate interplay between psychosocial and neurobiological factors. Hypotheses about the role of gender-specific stressors, and gender differences in the expression of fears warrant further investigation. Sex-specific variance has been identified in numerous neurotransmitter systems. The serotonin system may be of particular importance, as most drugs used in the treatment of panic disorder enhance serotonin neurotransmission and alterations in the serotonergic system have been found in panic patients relative to healthy controls. It seems likely that female sex hormones are involved, as periods of fluctuating levels of estrogen and progesterone have been linked to increase or decrease of panic symptomatology.

There is converging support for a considerable genetic influence on the pathogenesis of PD with several genes, particularly the COMT and MAO_A genes, driving the disease risk in a female-specific manner. However, it is still not comprehensively understood how these genes act to confer disease risk on a functional level, in interaction with one other as well as with environmental factors. Therefore, the currently identified genetic risk factors are of limited diagnostic or predictive value. However, genetic research may encourage further biochemical, physiological, or pharmacological efforts to develop innovative drugs for the treatment of PD, preferably in an individually tailored and gender-specific manner.

Identification of the psychosocial contributors and the biological substrates of gender-specific susceptibility for PD may be useful for better understanding the etiology of anxiety disorders in general.

Although gender differences have been found in the metabolism of anxiolytic drugs, it remains unclear whether this significantly affects treatment outcome. When treating panic disorder during pregnancy and lactation, a number of safety considerations have to be taken into account.

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Social Anxiety Disorder

Franklin Schneier and Julia Goldmark

Introduction

Social anxiety disorder (SAD), also referred to as social phobia, is characterized by persistent fear and avoidance of social situations due to fears of evaluation by others. SAD can be highly distressing, and it can interfere with school, work, and social life as sufferers avoid social or performance situations. Although many individuals with SAD report that their level of anxiety varies with the gender of those with whom they interact, and it has long been observed that men are overrepresented among patients seeking treatment for SAD relative to other anxiety disorders, there has been little study of gender differences in SAD. The gender literature that does exist for SAD, however, offers interesting implications for researchers and clinicians. This chapter will provide an overview of SAD with a specific focus on evidence for gender differences within this disorder.

Epidemiology

Prevalence, Demographics, and Clinical Features

Large epidemiological studies have established that SAD is one of the most common psychiatric disorders. The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), for example, recently found a lifetime prevalence of 5.0 % and 12-month prevalence of 2.8 % for SAD among 43,093 adults in the

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United States (Grant et al. 2005). A recent review (Fehm et al. 2005) of 21 community studies in European countries found median lifetime and 12-month prevalence rates of SAD of 6.7 % and 2.0 %, respectively. The WHO World Mental Health (WMH) Survey Initiative (Stein et al. 2010) found that lifetime social fears are common in both developed (15.9 %) and developing (14.3 %) countries; however, lifetime SAD has a higher prevalence in developed countries (6.1 %) compared to developing countries (2.1 %).

Mean age of onset is in the mid-teens, and onset after age 30 is uncommon (Schneier et al. 1992). Although prevalence of SAD is greatest among young adults, for many sufferers the disorder is chronic. Prevalence is also greater among persons who are less educated and those who are single (Schneier et al. 1992; Blanco et al. 2011). Additionally, SAD is usually accompanied by comorbid disorders, such as depression, substance abuse, or other anxiety disorders, which can further impair functioning (Fehm et al. 2005).

SAD has been shown in many studies to be associated with impairment and disability. SAD increases the risk of dropout from school, work absence, unemployment, and utilization of social welfare, causing significant financial costs for society (Lecrubier et al. 2000). When compared with persons with no psychiatric disorder, having SAD is associated with financial dependency and increased rates of suicidal ideation (Schneier et al. 1992; Cougle et al. 2009; Olfson et al. 2000). Katzelnick et al. (2001) examined costs and impairment associated with SAD in a community sample of 1,017 subjects. Subjects with generalized SAD and no comorbidity reported significant impairment in terms of family relations, romantic relationships, social network, and ability to moderate alcohol use, compared to those with no diagnosis. Generalized SAD was associated with significantly lower health-related quality of life, work productivity and earnings, and greater utilization of health services. During the month before participating in the survey, 12.2 % of subjects with SAD reported having had thoughts of suicide.

Several subtypes of SAD have been described. Generalized SAD has been the most studied subtype, and it was defined in DSM-III-R and DSM-IV by fear of most social situations (American Psychiatric Association 2000). Persons with generalized SAD tend to have more severe symptoms and impairment, and are more likely to seek treatment. The National Comorbidity Survey (1998) reported significantly greater comorbidity among persons with SAD and at least one feared situation other than public speaking. Persons with SAD involving three or more social fears also evidenced greater chronicity and impairment. Most persons with the nongeneralized type of SAD, or with the performance type newly described in DSM-5 (American Psychiatric Association 2013), have predominantly fears of performance such as public speaking, with relative sparing of social interaction situations.

Gender Differences in Community Samples

Prevalence of SAD among women has been found to be elevated relative to the rate in men in most community studies. In the NESARC study (Grant et al. 2005), 12-month prevalences were 2.1 % for men and 3.3 % for women; lifetime

prevalences were 4.2 % for men and 5.7 % for women. Similarly, elevated rates of SAD in women have been reported in European samples (Fehm et al. 2005). The female-to-male ratio of 1.35 for lifetime prevalence of SAD in the NESARC study (Xu et al. 2012) is within the range of previous epidemiological studies (Kessler et al. 1994; Ohayon and Schatzberg 2010). The ratio is lower, however, than gender ratios reported for other anxiety disorders in major epidemiologic studies, which have ranged from 1.8 for generalized anxiety disorder in the National Comorbidity Survey (Kessler et al. 1994) to 2.7 for agoraphobia in the Epidemiological Catchment Area (Bourdon et al. 1988). Xu et al. (2012) also found that men with SAD were more likely than women with SAD to have never been being married, or to be separated or divorced.

Crome et al. (2012) sought to investigate whether the preponderance of women among those diagnosed with SAD by community surveys was due to a response bias of women being more likely to respond positively to questions about SAD. The study involved a subsample of 1,755 participants in the Australian National Survey of Mental Health and Wellbeing who had reported at least one social fear. A series of factor analyses suggested that men and women tended to respond comparably to SAD diagnosis items. Men, however, tended to report lower levels of physical symptoms at low levels of social fear, compared to women. Overall, findings supported the legitimacy of higher rates of SAD among women.

Gender differences among persons with SAD were examined in a recent cross-sectional study by MacKenzie and Fowler (2013) of 36,984 Canadians aged 15–80 years. Men with SAD were more likely to be single, unattached, and living alone than women with SAD. Women with SAD were more likely to be widowed, separated, or divorced, and they were more likely to be a single parent. Women also reported poorer mental health and greater stress levels than men with SAD.

Several studies have examined the course of SAD in women and men. Gender differences in prevalence of SAD were small in the pre-school and elementary school years but increased after the age of 12, according to a retrospective study of 8,116 Canadian adults (DeWit et al. 2005). For persons with the generalized subtype of SAD, at every age from pre-school to early adulthood, the proportion of females who had developed SAD exceeded the proportion of males. In contrast, a female preponderance for the development of *nongeneralized* SAD began to emerge only after the age of 12. In a study of 2,128 Swedish students aged 12–14, the prevalence of SAD was 6.6 % among girls versus 1.8 % among boys (Gren-Landell et al. 2009), and 91.4 % of the children with SAD reported impairment in school functioning.

Gender differences in the prevalence of specific types of social fears have also been reported. A survey of 526 community respondents (Stein et al. 1994) showed that women reported significantly greater anxiety about public speaking, speaking to strangers, meeting new people, and dealing with people in authority, but that men and women did not differ significantly in severity of anxiety while writing in front of others, eating in front of others, or attending social gatherings. Women with SAD in the community also experienced higher rates of some social fears (Xu et al. 2012). Men and women with lifetime SAD differed significantly in rates of fear of dating (men 29.5 % vs. women 22.3 %), being interviewed (men 39.7 % vs. women 52.0 %), and speaking at a meeting (men 69.4 % vs. women 74.9 %).

Several community studies have examined gender differences in comorbidity among individuals with SAD. Xu et al. (2012) found that men with a lifetime diagnosis of SAD were more likely to have lifetime alcohol abuse and dependence, drug abuse and dependence, pathological gambling, conduct disorder, and antisocial personality disorder. Women were more likely to suffer from mood and anxiety disorders, except bipolar I and II disorders, which had the same probability to be diagnosed in both genders. Women with SAD were thus more likely to have comorbid internalizing disorders and less likely to have comorbid externalizing disorders.

Rodebaugh et al. (2012) examined the impact of psychiatric disorders on friendship quality by gender, among participants in the National Comorbidity Survey (Kessler et al. 2004). SAD had a negative effect on friendship quality in both men and women, although in men this was exacerbated when comorbid generalized anxiety disorder was present, whereas in women comorbid major depression was associated with an additional negative impact on friendship quality.

In adolescents, a Finnish study (Väänänen et al. 2011) found gender differences in the longitudinal relationship between SAD and depression. In this population-based prospective study of 15-year-olds ($N = 2{,}038$), SAD at baseline increased the risk for depression over the next 2 years in boys only. Among adolescent girls, baseline depression was a risk factor for subsequent SAD. Wu and colleagues (2010) looked at gender differences in the relationship between SAD and substance use among 781 adolescents in the community. In girls, there was a trend for SAD to be associated with lower rates of substance use. In boys, however, cigarette smoking was significantly associated with SAD.

Buckner and colleagues have further investigated the interactions between SAD, substance use disorders, and gender. In one study, Buckner et al. (2006) examined the relationship between cannabis use disorder, SAD, and peer influence in 123 male and female undergraduates. Symptoms of SAD were significantly related to symptoms of cannabis use disorder only among women. This relationship was further moderated in women by the influence of peers and their use of alcohol and cannabis. Specifically, women with more SAD symptoms were particularly prone to problematic cannabis use and more vulnerable to influences from peers. In another study (Buckner and Turner 2009), SAD was a risk factor for development of alcohol use disorders among women only, in a 3-year prospective study of 1,803 young adults from the National Comorbidity Survey. The risk of women developing an alcohol use disorder was further moderated by lower family cohesion and more adverse family relations.

In respect to treatment seeking, individuals with SAD typically do not seek treatment until their late 20s to 30s, despite a mean age of onset of SAD in early adolescence (Mannuzza et al. 1995). Xu et al. (2012) reported that among persons with lifetime SAD in the community, men and women did not differ in their overall probability of treatment seeking for SAD. Lifetime rates of treatment seeking for SAD were 17.9 % for men and 19.2 % for women; lifetime rates of use of medication for SAD were 8.8 % for men and 12.4 % for women. Thus, over 80 % of individuals with SAD in the NESARC study had received no treatment for it, and the mean age at first treatment was 27.2 years (Grant et al. 2005).

Gender Differences in Clinical Samples

There have been relatively few studies of gender differences in clinical samples of SAD patients. One study assessed gender differences in SAD features and treatment outcome in an anxiety clinic sample with 108 men and 104 women, of whom a similar proportion of men and women had received a diagnosis of SAD (63.9 % vs. 71.2 %) (Turk et al. 1998). Among patients with SAD, men and women reported suffering from SAD for similar lengths of time (19.3 vs. 20.3 years). There were no significant differences in the proportions of men and women who reported previous psychotherapy (61.6 % vs. 63.6 %) or treatment with pharmacotherapy (38.4 % vs. 31.8 %). Men and women did not differ significantly in rates of comorbid mood disorders (21.9 % vs. 27.3 %) or anxiety disorders (38.4 % vs. 48 %). Women reported more severe social fears and differences in pattern of feared situations, however. Women reported significantly greater fear in situations of talking to authority figures, performing/giving a speech in front of an audience, working while being observed, entering a room while others are already seated, being the center of attention, speaking up at a meeting, expressing disagreement or disapproval to people they do not know very well, giving a report to a group, and giving a party. Men reported significantly more fear than women when urinating in public bathrooms and returning goods to a store.

Yonkers and colleagues (2003) studied a sample of 66 men and 96 women patients with SAD who were participating in an 8-year naturalistic study. There was a nonsignificant trend for onset of SAD to have occurred at an earlier age in women, 14 years, compared to 16 years for men. The probability of remission of SAD over the follow-up period of up to 8 years was only 31 % and did not differ by gender. Among 105 adolescent patients with a gender identity disorder, there was a higher rate of SAD in those who had been assigned male gender at birth (15.1 %) than those who had been assigned female gender (3.8 %) (DeVries et al. 2011). Ham et al. (2005) examined perceived social support quantity and satisfaction in 23 women and 28 men seeking treatment for SAD. Men and women did not differ on measures of social support. Among the women with SAD, however, younger, unmarried women reported having smaller social support networks and less satisfaction with their social support networks than older, married women. This pattern was not present among the socially anxious men. Randall and colleagues (2000) compared 110 male and female patients with SAD and alcohol use disorders. Women had higher fear ratings on SAD measures compared to men. They also experienced more distress in social and family functioning and had a higher rate of psychiatric comorbidity.

Psychobiology

Neural Circuitry

A growing number of neuroimaging studies of SAD during the last decade have attempted to elucidate the neural mechanisms of the disorder. The most consistent findings have demonstrated increased activation of the amygdala and surrounding

cortices, including the hippocampus (Schmidt et al. 2010) in persons with SAD during exposure to emotional threat stimuli, such as angry faces. Functional neuroimaging studies have reported that exaggerated amygdala activation is positively correlated with symptom severity and decreases after successful treatment (Furmark et al. 2002). Furthermore, treatment studies indicate that both pharmacotherapy and psychotherapy of SAD normalize activation in the amygdala and related structures (Goldin and Gross 2010).

Pathophysiology

A variety of neurotransmitter systems, including serotonin, norepinephrine, dopamine, GABA, and glutamate have evidenced abnormalities in SAD. Dysfunction of the hypothalamic-pituitary-adrenal axis has also been reported. Few of these studies, however, have assessed outcome by gender. In a study of 53 patients seeking treatment for SAD, however, heart rate variability, an index of autonomic control, was reduced in SAD overall, but also more specifically among women with SAD (Alvares et al. 2013). This may indicate a greater sensitivity to the effects of social anxiety on parasympathetic nervous system reactivity in women.

The prototypical onset of SAD in early adolescence has raised questions about the impact of physiological and psychosocial changes of puberty. Deardorff et al. (2007) assessed 106 children aged 9–11 for pubertal status and social anxiety. Advanced pubertal development was associated with higher levels of social anxiety among girls only, consistent with findings of gender differences in depression.

Genetics and Family Studies

Family studies have shown that SAD is familial (e.g., Lieb et al. 2000), with first-degree relatives of adults with SAD being three times as likely as relatives of control subjects to suffer from SAD (Fyer et al. 1995). Some studies have further suggested that the generalized subtype may be more familial than the specific subtype (Stein et al. 1998). Part of this familial risk is attributable to genetic heritability, and twin studies suggest that the underlying structure of the genetic and environmental risk factors is similar between men and women (Hettema et al. 2005).

Genetic influences on the development of SAD may be specific to the disorder, or may be related to relatively nonspecific factors, such as negative affect. A highly heritable temperamental trait that is thought to predispose individuals to SAD is behavioral inhibition, characterized by a consistent pattern of behavioral, physiological, and emotional responses to unfamiliar people and novel situations. Inhibited children usually respond with restraint and withdrawal to novel objects and situations, and they are usually shy with unfamiliar people (Kagan 1994). In a longitudinal study of 238 children, girls evidenced greater inhibition and afternoon cortisol levels as preschoolers, and they were at greater risk for developing chronic high inhibition and SAD (Essex et al. 2010).

Psychological Aspects of Pathogenesis

Psychosocial factors, such as parenting, peer interactions, and culture can play an important role in the development of SAD. Socially anxious adults often report having experienced negative parenting qualities such as overprotection, lack of warmth, excessive concern with the opinion of others, and rejection during their childhood (Caster et al. 1999). Adults with SAD are more likely to recall their parents as excessively protective and controlling (Rapee and Melville 1997).

Childhood maltreatment has been associated with symptom severity, reduced quality of life, and impaired functioning in adults with SAD (Bruce et al. 2012). Data were obtained from 156 treatment-seeking patients with a primary diagnosis of generalized SAD who had a history of childhood trauma. Childhood emotional abuse, emotional neglect, and physical neglect, but not sexual or physical abuse, predicted more severe symptoms in patients with SAD. Of the maltreatment subtypes, emotional abuse was the strongest predictor of severity of social anxiety, disability, and decreased quality of life. Other studies have linked SAD with early sexual abuse. Feerick and Snow (2005) examined the relationship between childhood sexual abuse and SAD in a sample of 313 undergraduate women. In this study, 31 % of the women reported that they had experienced some form of sexual abuse in childhood. Women with a history of sexual abuse reported more symptoms of anxiety and distress in social situations than women who had not experienced sexual abuse. Those women whose abuse included actual or attempted intercourse had higher scores for social avoidance than women who had not been abused, or who had experienced other forms of abuse such as exposure or fondling. In addition to the type of abuse experienced, earlier age of onset of abuse also significantly predicted greater avoidance and distress in adulthood.

McGabe et al. (2003) found a relationship between bullying in childhood and adolescence and SAD later in life. This study assessed the relationship between childhood memories for teasing and SAD in adulthood. Five hundred and fourteen undergraduates completed a questionnaire that measured the degree to which people recall having been teased during childhood and also completed established measures of SAD. Men and women recalled having been teased with similar frequency; however item-by-item analysis suggested that boys had a more negative experience with teasing than girls (e.g., men remembered having been teased about not doing well at school and being a troublemaker more often than women).

Parents impact their children's social interactions directly by arranging play dates, overseeing play situations, and supervising peer interactions (Masia and Morris 1998). Thus, parents' relationships and skills related to their child's development could influence their social and emotional development. Maternal SAD has been shown to significantly predict SAD in offspring (Bögels et al. 2001). Although most of the research on parenting has focused on mothers, paternal influences may also be important (Greco and Morris 2002). The influence of fathers is smaller, however, and more significant later in the child's life (Connel and Goodman 2002).

Contemporary theories of SAD emphasize the role of cognitive processes in the maintenance of the disorder, and a theoretical model has been proposed

(Clark and Wells 1995). According to this model, individuals with SAD are apprehensive in social situations because they perceive the social standard as being high and they doubt that they are able to make a favorable impression, which will result in disastrous consequences (Leary 2001). This leads to a further increase in apprehension and increased self-focused attention, which triggers a number of additional cognitive processes (Hirsch and Clark 2004). As a result, the individual with SAD anticipates social mishaps and engages in avoidance and/or safety behaviors (Wells et al. 1995).

Avoidance and safety behaviors play an important role in the maintenance of SAD, because they reinforce social fears and diminish opportunities for positive social experiences. Individuals with SAD engage in safety behaviors in social situations in order to minimize negative evaluations from others; typical examples of safety behaviors include avoiding eye contact, monitoring one's speech, and avoiding pauses while talking (Kim 2005). When safety behaviors are used, the individual attributes the nonoccurrence of feared catastrophes to the implementation of the safety behavior. Therefore, safety behaviors are maladaptive, because they prevent exposure to the feared social situations and processing of the emotional information, for example, individuals who speak little in social encounters because they fear negative evaluation are less likely to receive positive feedback from others (Clark 2001).

In addition to the previously mentioned cognitive and behavioral factors that contribute to the development and/or maintenance of SAD, recent evidence also suggests a contributing role of exaggerated negative emotional reactions, attenuated positive emotional reactions, and emotion regulation difficulties in producing functional impairment (Goldin et al. 2009). While there are numerous ways of affecting one's emotional experiences, two specific strategies have received substantial scientific attention: cognitive reappraisal and emotion suppression. Cognitive reappraisal involves changing one's perspective to downplay or enhance a situation's emotional impact and altering the interpretation of emotional information (Gross 2002). Emotion suppression involves inhibiting emotional responses to a situation by downregulating the expression of the emotion. People with SAD report frequently suppressing both positive (Werner and Gross 2010) and negative emotions (Erwin et al. 2003). Excessive use of suppression can have negative impact on the positive experiences of people with SAD. A meta-analysis of 19 studies found a stable, moderate relationship between SAD and less frequent and intense positive emotions (Kashdan 2007). Maladaptive emotion regulation contributes to the adverse impact of social anxiety on positive events in daily life, and people high in SAD report using more positive emotion suppression (Turk et al. 2005). One reason for this may be that individuals with SAD find expressing positive emotions in social-evaluative situations to be uncomfortable (Kashdan et al. 2011). While suppressing positive emotions may help individuals with SAD to minimize social attention towards them, it may also contribute to sustained anxiety and avoidance of interactions.

Diagnosis

DSM-5

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association 2013), offers operationalized criteria for the diagnosis of psychiatric disorders by clinicians and researchers. In 2013, the publication of the Fifth Edition of the DSM incorporated several changes to the criteria for SAD (Heimberg et al. 2014). First, while "social anxiety disorder" had been previously considered a secondary name for "social phobia," it is now recognized in DSM-5 as the principal name for this diagnosis, because it was felt to better convey the sense of pervasiveness and impairment associated with the disorder. The description of primary fear in SAD was broadened beyond showing embarrassing or humiliating anxiety symptoms, to include fear of showing symptoms that will be negatively evaluated. Whereas DSM-IV required that the person must recognize that the fear is excessive or unreasonable, DSM-5 instead requires that the fear be out of proportion to the actual threat, and encourages consideration of cultural context. Another change was to allow the diagnosis of SAD to be made in the presence of another embarrassing medical condition, as long as the social anxiety symptoms are either unrelated to the medical condition or excessive, in the clinician's judgment.

DSM-5 criteria for SAD require two key features:

- A marked fear or anxiety about social situations or performance situation in which scrutiny by others could occur. For a child to be diagnosed, the anxiety must occur with peers, and not only with adults.
- The individual fears showing behaviors or anxiety symptoms that will result in negative evaluation by others, and experiences such as embarrassment or rejection by others.

In addition, DSM-5 criteria require that the social situations must almost always provoke fear or anxiety, and the situations are avoided or endured with fear and anxiety. The fear or anxiety must be out of proportion to the actual threat posed by the social situation. Symptoms must have persisted for at least 6 months or more, and they must cause clinically significant distress or impairment in social or occupational functioning. Finally, social anxiety and avoidance cannot be due to the physiological effects of a drug of abuse, a medication, or another medical condition. It also must not be better explained by the symptoms of another mental disorder, such as when social avoidance occurs in depression due to lack of social interest. Social anxiety disorder can be diagnosed in the presence of another potentially embarrassing medical condition, such as essential tremor or disfigurement from burns, if the fear, anxiety, and avoidance are unrelated to the medical condition or is excessive.

ICD-10

The International Classification of Disease, 10th Edition (ICD-10) criteria for social phobia, developed by the World Health Organization (WHO) are as follows:

All of the following criteria should be fulfilled for a definite diagnosis:

(a) The psychological, behavioral, or autonomic symptoms must be primarily manifestations of anxiety and not secondary to other symptoms such as delusions or obsessional thoughts.
(b) The anxiety must be restricted to or predominate in particular social situations.
(c) The phobic situation is avoided whenever possible.
Includes: anthrophobia; social neurosis

Differential Diagnosis

Below we briefly review some of the clinical issues in distinguishing SAD from other common conditions. In addition to trying to distinguish SAD from related disorders, it must be recognized that any of these conditions can also occur comorbidly with SAD.

Shyness Shyness is a personality trait that is not inherently pathological. While many persons with SAD may consider themselves shy, SAD differs in having a significant adverse impact on social, occupational, and other important areas of functioning.

Agoraphobia Individuals suffering from agoraphobia may fear and avoid social situations; however, their primary fear is that escape from a social situation may be difficult in the event of incapacitation or panic-like symptoms, whereas individuals with SAD are primarily fearful of the potential for scrutiny by others that is inherent in an interpersonal situation.

Panic disorde Individuals with SAD may have panic attacks, but such panic attacks are manifestation of their primary concern about fear of negative evaluation, and the panic attacks are limited to being in or thinking about a social situation. In panic disorder, panic attacks usually occur in situations both with and without others present, and the primary concern is about the panic attacks themselves, rather than fear of scrutiny.

Generalized anxiety disorder Social worries are common in generalized anxiety disorder, but they constitute just one focus among broader concerns that may include worries about health, money, and safety.

Separation anxiety disorder Individuals with separation anxiety disorders may avoid social settings because of concerns about being separated from attachment figures. People with separation anxiety disorder are generally comfortable in social settings when the attachment figure is present or when they are at home.

Specific phobia Individuals with specific phobias may fear humiliation or embarrassment secondarily to their primary phobia (e.g., embarrassment about being seen fainting when blood is drawn), but they do not more generally fear negative evaluation in other public or social situations.

Major depressive disorder Individuals with major depressive disorder may be concerned about negative evaluation because they feel they are not worthy of being liked, and they may avoid social situations out of lack of motivation and interest.

Body dysmorphic disorder Individuals with body dysmorphic disorder are preoccupied with perceived flaws in their physical appearance that are not observable to others. They are primarily concerned with their own evaluation of these flaws, rather than by negative evaluation by others.

Psychotic disorders Individuals with psychotic disorders may avoid interpersonal situations due to paranoid belief of the threat of harm from others. Persons with SAD, however, generally have good insight that their beliefs are out of proportion to the actual threat posed by the social situation.

Autism spectrum disorder Social anxiety and social communication deficits are hallmarks of autism spectrum disorder. However, individuals with SAD usually have adequate age-appropriate social relationships and capacity for social communication.

Personality disorders Due to its frequent onset in childhood and persistence into adulthood, SAD shares features with personality disorders. Avoidant personality disorder criteria greatly overlap those of SAD, so they often co-occur, especially among persons with more severe and pervasive SAD.

Eating disorder Persons with anorexia or bulimia nervosa may have excessive concerns about negative evaluation related to their body image or secondary to others observing their problematic eating behavior. In persons with SAD, however, social fears are not limited to concerns about body image or eating behaviors.

Medical conditions that draw unwanted attention Medical conditions can produce symptoms that may be embarrassing for some sufferers (e.g., trembling in Parkinson's disease). These persons are not diagnosed with SAD unless the symptoms of SAD are out of proportion to that expected from the level of the symptoms of their other medical condition.

Evaluation

As patients with SAD often present with other symptoms, such as depression, and they sometimes initially minimize social anxiety symptoms that have often been highly chronic, an evaluation should proactively probe functioning across a variety of social situations to map the scope of the disorder. Rating scales may be helpful in assessing severity of SAD and monitoring improvement during treatment. One of the most commonly used measures to assess symptom severity in SAD is the Liebowitz Social Anxiety Scale, which assesses fear and avoidance of 24 social situations. It can be administered by a clinician or self-rated, has good internal consistency, and correlates with other measures of social anxiety (Heimberg et al. 1999). The Social Interaction Anxiety Scale (Mattick and Clarke 1998) is a self-report measure that consists of 20 items and evaluates anxiety experienced in dyadic and group interactions. The Social Phobia Scale (Mattick and Clarke 1998) is another self-report measure that assesses fear of performance and observation situations.

Evaluation of SAD should take into account developmental factors. Increases in fears of social evaluation are part of normal development; however, for some children and adolescents these fears become extreme and do not dissipate over time. The vast majority of children and adolescents with SAD go unrecognized by both parents and professionals, including school personnel. When recognized, the diagnosis and assessment of SAD among children and adolescents is complicated by several factors. First, children's and adolescents, level of cognitive development affects the degree to which they are able to articulate concerns and fears of humiliation, which is more difficult for younger children (Southam-Gerow and Kendall 2000). Second, the manifestation of SAD varies by age. Younger children have more crying and episodic illusions, such as being looked at and talked about by strangers (Abe and Suzuki 1986), whereas adolescents present more externalizing problems such as fighting, truancy, and covert antisocial behavior (Davidson et al. 1994). Third, boundaries between normal and pathological fears are often ambiguous, especially in adolescence in which concerns about peer acceptance and body image are common (Petersen and Leffert 1995).

Pharmacotherapy

Pharmacotherapy, along with CBT and other psychotherapies discussed below, constitutes one of the most common modalities of treatment for SAD. Below we review the main classes of medications that have evidence for efficacy in SAD. These include the serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), benzodiazepines, monoamine oxidase inhibitors, and others.

Serotonin reuptake inhibitors are the first-line medication option for treatment of SAD, based on evidence from over 20 randomized controlled trials (RCTs) of five medications within this class. Paroxetine, sertraline, and fluvoxamine are FDA-approved for the indication of SAD in United States. The serotonin-norepinephrine reuptake inhibitor venlafaxine has also been FDA-approved for SAD on the basis of

several RCTs. A meta-analysis of medication trials found that, relative to placebo, treatment response was superior for the SSRIs ($N=19$ studies; relative risk of response (RR) = 1.69; 95 % CI: 1.49, 1.90; Total sample $N=4{,}615$) and for venlafaxine ($N=4$; RR = 1.59; 95 % CI: 138, 1.83; $N=1{,}173$) (Ipser et al. 2008).

Treatment with SSRIs and SNRIs is dosed similarly to dosing used in depression (i.e., median effective paroxetine dose 20 mg/day). An adequate trial of SSRI or SNRI medication may require 8–12 weeks to assess efficacy (Stein et al. 2002). Advantages of SSRIs include a relatively mild adverse-effect profile, safety in overdose or with concurrent use of alcohol, and a broad spectrum of efficacy for comorbid anxiety and affective disorders. Common side effects include nausea and sexual dysfunction.

The benzodiazepines have been far less studied for SAD, but the best evidence for efficacy in this class exists for clonazepam. Davidson et al. (1993) reported that in a 10-week double-blind, placebo-controlled study of clonazepam in 75 patients, 78 % of those on clonazepam (mean standing dose of 2.4 mg/day) and 20 % of those on placebo were rated as at least moderately improved. Another randomized clinical trial found that clonazepam and cognitive-behavioral group therapy were equally effective after 12 weeks of treatment (Otto et al. 2000). In a placebo-controlled discontinuation trial among SAD patients effectively treated with clonazepam, 79 % were able to tolerate slow taper (0.25 mg reduction every 2 weeks) and discontinuation without relapse (Connor et al. 1998). Benzodiazepines are a second-line medication treatment due to their lack of efficacy for comorbid depression, risk of abuse, contraindication in the presence of comorbid substance abuse, potential adverse effects on cognition and coordination, and routine development of physiological dependence requiring slow taper when drug is to be discontinued.

The monoamine oxidase inhibitors (MAOIs) are another class of medications that have appeared efficacious in multiple RCTs, but they are reserved for refractory cases due to dietary restrictions and risk of serious side effects (see Schneier 2011 for more complete review of SAD pharmacotherapy). Reversible inhibitors of monoamine oxidase, such as moclobemide, appear safer but probably less efficacious. Other medications with evidence of efficacy in at least one RCT include the antidepressant mirtazapine and the alpha-2-delta calcium channel agents gabapentin and pregabalin.

Reviews of medication treatment of SAD generally have not found gender to be a significant moderator of treatment response (e.g., Stein et al. 2004). An exception to this was the two-site RCT of gabapentin (Pande et al. 1999), in which placebo-treated women had higher response rates than placebo-treated men (42 % vs. 0 %), but genders did not differ in response rates to active gabapentin.

Psychotherapy

Cognitive-behavioral therapy (CBT) is the most comprehensively studied psychotherapeutic method for treatment of SAD, and its effectiveness has been established in multiple RCTs (Heimberg 2002). CBT is commonly comprised of

two main components: exposure, which involves strategies to confront feared situations and to test for feared consequences by conducting behavioral experiments, and cognitive restructuring, with the goal of challenging maladaptive cognitions and developing more helpful coping thoughts. CBT is typically conducted weekly over a 3–6 month period, in group or individual format. After initial psychoeducation, the patient and therapist develop a hierarchy of anxiety-provoking situations. Exposures typically begin with one of the least feared situations and then gradually approach more difficult situations as a sense of mastery is achieved.

In the cognitive restructuring component of CBT, individuals are taught to:

1. Identify negative thoughts related to the anxiety-provoking situations
2. Evaluate the accuracy of their beliefs
3. Derive alternative thoughts based on the information

Several meta-analyses of a variety of CBT support the clinical efficacy of CBT for SAD (Federoff and Taylor 2001; Feske and Chambless 1995; Taylor 1996). Effectiveness of social skills training and cognitive restructuring without exposure were evaluated in three meta-analyses (Federoff and Taylor 2001; Taylor 1996). These treatments yielded more modest effect sizes.

Other forms of psychotherapy have received support for efficacy but have been less studied. Mindfulness and acceptance-based therapies emphasize present-moment focus and a nonjudgmental awareness of cognitive, emotional, and physiological processes (e.g., Kabat-Zinn 2003). Interpersonal Psychotherapy (IPT), which focuses on correcting dysfunctional patterns in interpersonal relationships, is a time-limited approach that employs specific techniques, such as reassurance, role-playing, and control of emotions. In psychodynamic therapy for SAD, the patient is encouraged to examine beliefs about negative judgment and abandonment (Leichsenring et al. 2013).

Gender has not been shown to moderate outcome of psychotherapy, but psychotherapists need to be sensitive to how a patient's culture may influence attitudes about approaching others of the opposite sex, or how an office subculture's attitudes about gender may impact a patient's efforts to increase assertiveness. Turk et al. (1998) also noted that evidence for gender differences in pattern of social fears supports the practice of attending to the gender composition of therapy groups when CBT for SAD is offered in group format. They observed that men and women with SAD more easily identify with the experiences of same-gender peers, and therefore treatment groups that have a very small number of male or female participants put the underrepresented gender at risk for dropping out. Additionally, offering feedback in the form of reviewing videos of CBT exposures has been reported in some studies to help patients become aware of the discrepancy between their beliefs about their behavior versus their actual social performance. One report, however, suggests that use of video feedback in CBT may be less effective in men (Chen et al. 2010).

Conclusions

A growing body of studies has explored gender differences in SAD, one of the most common anxiety disorders. SAD, like most anxiety and depressive disorders, is more common among women overall. Although women in the community do not report lesser severity of SAD or lesser rates of treatment seeking, clinical samples of SAD have often been found to include equal representations of men and women, or even a predominance of men. Men are more likely to report dating problems, whereas women have higher rates of difficulty speaking up in groups or work situations. Women are more likely to experience comorbid internalizing disorders, and men are more likely to have substance use disorders. It is likely that these patterns of difference reflect differences in both societal influences and physiology.

A smaller number of developmental studies suggest that a variety of gender-related influences play a role in the development of SAD. These range from the psychosocial, such as increased rates of abuse among girls, to complex influences, such as the combined hormonal and social mechanisms by which early puberty may lead to increased social anxiety in girls, to physiological differences in cortisol and heart rate variability. The findings highlight the need for further research to disentangle the complicated influences of gender on SAD, and the importance for clinicians to be sensitive to potential gender differences in etiology and the need to target treatments to the personal characteristics of the individual.

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Obsessive-Compulsive Disorder

Lauren S. Hallion, Laura E. Sockol, and Sabine Wilhelm

Introduction

Previously classified as an anxiety-related disorder, obsessive-compulsive disorder (OCD) was moved to a new "Obsessive-Compulsive and Related Disorders" section in the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*; American Psychiatric Association [APA], 2013). This section also includes body dysmorphic disorder (BDD), hoarding disorder (previously considered a subtype of OCD), trichotillomania (hair-pulling disorder), and excoriation (skin-picking disorder; APA 2013). In *DSM-5*, OCD is characterized by the presence of obsessions and compulsions (Criterion A), which must be time-consuming or cause clinically significant distress or impairment (Criterion B; APA 2013, p. 238). *Obsessions* are egodystonic "repetitive and persistent thoughts, images, or urges" (APA 2013, p. 238), while *compulsions* are "repetitive behaviors … that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly" (APA 2013, p. 237). Whereas obsessions are strictly mental activities, compulsions can be observable (e.g., checking locks or washing hands) or covert (e.g., counting or mentally repeating certain words or phrases).

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Epidemiology

OCD is a relatively common disorder, affecting 1–3 % of the general population in a given year (Apter et al. 1996; Ruscio et al. 2010). Approximately half of all treatment-seeking adults with OCD are women (Rasmussen and Eisen 1992). In community samples, women represent slightly more than half of all adults with OCD (Bebbington 1998). In pediatric samples, the gender difference is skewed toward males, with an approximately 2:1 male-to-female ratio (e.g., Hanna 1995). This difference may reflect the earlier modal age of onset for OCD in males (modal age 13–15) compared to females (20–24; Rasmussen and Eisen 1990).

Several gender differences in OCD phenomenology have been identified. For example, women are more likely than men to report obsessions focusing on contamination (e.g., fears of spreading or contracting illness) and corresponding cleaning compulsions (e.g., excessive hand-washing and cleaning; de Mathis et al. 2011). This gender difference appears to be stable across cultures, indicating that biological factors or cross-cultural gender role norms may play a role in OCD presentation (de Mathis et al. 2011). Conversely, sexual obsessions (e.g., fears of pedophilia and homosexuality) are more frequently observed in men than women, as are ordering and symmetry obsessions (Lensi et al. 1996).

Gender differences in OCD-related impairment have also been identified. In a large Brazilian sample (Torresan et al. 2013), men with OCD were more likely than women to be single (61 % of men vs. 47 % of women), to be unemployed (20 % vs. 14 %), and to live with their family of origin or in assisted living facilities (50–66 % vs. 20–40 %). Although some studies have reported that OCD symptoms are more severe in women on average (Torresan et al. 2013), other studies have found no gender differences in OCD severity (Labad et al. 2008).

Subtypes

Perinatal OCD

Intrusive thoughts and compulsive behaviors similar to those that characterize OCD are common among new and expectant parents (Abramowitz et al. 2003a, b; Fairbrother and Abramowitz 2007; Zambaldi et al. 2009). Prevalence estimates of OCD during pregnancy range from 0.2 % (Zar et al. 2002) to 29 % (Chaudron and Nirodi 2010), with many studies reporting prevalence estimates in the range of 1–2 % (Russell et al. 2013). Onset of OCD after the birth of a child (often called postpartum OCD) is more likely to occur in women than men (13 % vs. 6.5 % of individuals with OCD; Torresan et al. 2013). During the postpartum period, prevalence estimates range from 0.7 % (Navarro et al. 2008) to 9 % (Zambaldi et al. 2009), with many estimates in the 2–4 % range (Russell et al. 2013). A recent meta-analysis estimated the prevalence of OCD to be 2.1 % during pregnancy and 2.4 % during the first year postpartum; this review found that the perinatal period is associated with a 79 % increase in risk for OCD compared to the general female population (Russell et al. 2013).

Among individuals with OCD, pregnancy and childbirth are commonly nominated as events precipitating the onset of symptoms (Maina et al. 1999). Among women with preexisting OCD, there does not seem to be a consistent relationship between pregnancy and OCD symptoms (Forray et al. 2010; Williams and Koran 1997). However, many women with OCD report that their symptoms worsen during the postpartum period (Labad et al. 2005; Williams and Koran 1997).

Interestingly, the content of obsessions and compulsions in this population appears to be influenced by the perinatal context. OCD with onset during pregnancy is commonly characterized by contamination obsessions and corresponding washing and cleaning compulsions, while OCD with onset during the postpartum period is commonly associated with harm obsessions and corresponding checking or avoidance compulsions (Buttolph and Holland 1990; Sichel et al. 1993). Obsessions related to harming the infant can be distinguished from infanticidal ideation that may occur in severe postpartum depression or psychosis by the egodystonic nature of the obsessions; women with postpartum OCD often engage in extensive avoidance and rituals to address their fears of harming their infants (Abramowitz et al. 2003b). To date, no cases of a woman with "pure" OCD causing harm to her infant have been documented (Ross and McLean 2006).

H-OCD

One specific manifestation of OCD includes concerns related to sexual orientation, including doubts regarding one's sexual orientation and fears that one may be homosexual (H-OCD; Williams 2008). These symptoms are often misdiagnosed; obsessions related to sexual orientation are commonly misattributed to "latent homosexuality" or interpreted as indicative that the patient is actually uncertain of his or her sexual orientation (Williams 2008). In a sample of 409 patients in OCD specialty clinics, 8 % of the sample reported current obsessions related to sexual orientation and 3.9 % endorsed a lifetime history of these obsessions; men were twice as likely to endorse these obsessions (Williams and Farris 2011).

Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections (PANDAS)

PANDAS is a pediatric variant of OCD, the defining feature of which is a sudden onset of OCD following a Group A *streptococcus* infection (Giedd et al. 2000). OCD-related PANDAS symptoms are similar to those found in classic pediatric OCD. Mood lability, personality changes, hyperactivity, tics, decreased handwriting quality, and other symptoms are also frequently observed (Murphy et al. 2012). To date, no large-scale epidemiological studies of PANDAS have been conducted. However, a recent study of 109 children ages 4–17 with OCD found that 41 of these children (68 % male) met criteria for PANDAS, suggesting a higher prevalence in boys than girls (Murphy et al. 2012). In that study, children with PANDAS were more likely than those with non-PANDAS OCD to report an episodic course characterized by full remission and subsequent "flare-ups," to show symptom remission during antibiotic therapy, and to have elevated streptococcal titers.

Comorbidity

The majority of individuals who meet criteria for OCD also meet criteria for at least one additional psychiatric disorder (Rasmussen and Eisen 1990; Steketee et al. 2001). In the National Comorbidity Survey-Replication study (NCS-R), 90 % of adult respondents who met lifetime DSM-IV criteria for OCD also met criteria for another lifetime disorder (Ruscio et al. 2010). The most common comorbid conditions were anxiety disorders, followed by mood disorders, impulse control disorders, and substance use disorders (Ruscio et al. 2010). Comorbid obsessive-compulsive and related disorders are also common (Richter et al. 2003).

Gender differences in patterns of comorbidity appear to reflect overall gender differences in the prevalence of psychiatric disorders. Women with OCD are more likely to present with comorbid eating disorders (Bogetto et al. 1999; Lochner et al. 2004; Torresan et al. 2009, 2013), major depression (Castle et al. 1995; Labad et al. 2008), and impulse control disorders (Bogetto et al. 1999; Torresan et al. 2009, 2013). Conversely, men are more likely to present with comorbid social phobia (Bogetto et al. 1999; Jaisoorya et al. 2009; Torresan et al. 2013; Tükel et al. 2004), tic disorders (Jaisoorya et al. 2009; Torresan et al. 2009, 2013), substance use disorders (Bogetto et al. 1999; Lochner et al. 2004; Torresan et al. 2013), and bipolar disorder (Bogetto et al. 1999; Lensi et al. 1996).

Many patients with OCD also meet criteria for at least one personality disorder (Baer and Jenike 1992; Steketee et al. 2001). The most common comorbid *DSM-IV* Axis II disorders are those on Cluster C, the "anxious cluster" (Steketee et al. 2001). There is some evidence that men with OCD report higher levels of traits associated with the Cluster C personality disorders than do women (Castle et al. 1995; Lensi et al. 1996).

Psychobiology

Neuropsychology

Although a growing body of research has investigated neuropsychological performance in OCD, few studies have explicitly examined sex and gender differences in these domains. The existing studies suggest few, if any, consistent sex differences in executive functioning and neuropsychological performance. One of the largest such studies (Mataix-Cols et al. 2006) examined performance on a wide range of neuropsychological tests in a sample of 33 men and 23 women with OCD and 40 healthy controls (50 % women, matched to the OCD sample on age, education level, and handedness). The study revealed a significant sex by group interaction for verbal fluency: Women with OCD performed more poorly than healthy control women; no difference was found for men. No significant interactions were observed for any other domain, including general nonverbal intelligence, attention, working memory, set-shifting, or inhibition.

A subsequent study using a similar sample (31 men and 19 women with OCD and a healthy control group matched for sex, age, education, and handedness;

Segalàs et al. 2010) did not replicate the previous finding of poorer verbal fluency among women with OCD. Instead, the study found poorer nonverbal memory performance in men with OCD compared to healthy control men. This difference was not observed for women. No interactions were found for verbal memory, general intelligence, attention, or working memory.

In several studies that did not explicitly examine gender, adults and children with OCD demonstrated deficits in response inhibition, defined as the ability to override a dominant or prepotent response (e.g., turning right to drive home) to make a less dominant, task-appropriate response (e.g., turning left to stop by the supermarket; Miyake et al. 2000). This finding does not appear to vary by sex (Kang et al. 2013). Impairments have also been observed in some studies of planning and decision-making, although other studies have failed to replicate these findings (Menzies et al. 2008). Other studies have found few or no impairments on a range of executive functioning tasks in individuals with OCD (Abramovitch et al. 2012).

Neurobiology

Neuroimaging research has revealed several brain regions and circuits that may play a role in the pathophysiology of OCD. Again, however, small sample sizes and a relative lack of research preclude strong conclusions about sex differences in these circuits. Leading neurobiological models of OCD focus on abnormalities in several interconnected brain regions, including the orbitofrontal cortex (OFC; particularly lateral and medial regions), anterior cingulate cortex (ACC, particularly dorsal regions), thalamus, and basal ganglia, which contains the striatum, nucleus accumbens, and other subregions (Graybiel and Rauch 2000; Milad and Rauch 2012).

The OFC is most commonly recognized for its role in emotional and motivational facets of behavior, including evaluating and monitoring changes in the reward value of a stimulus (Rolls 2004). Findings from structural and functional neuroimaging studies suggest several OCD-related abnormalities in the OFC and its subregions. Compared to healthy controls, adults with OCD tend to show reduced OFC volume (Menzies et al. 2008; Rotge et al. 2009) but increased glucose metabolism at rest (Harrison et al. 2009) and in response to symptom-provocation paradigms, wherein OCD symptoms are elicited in the scanner (Rotge et al. 2009). Notably, this hypermetabolism in the OFC and in several other regions is normalized following effective cognitive-behavioral therapy or pharmacotherapy for OCD (see Abramovitch et al. 2012 for a review).

The OFC is strongly interconnected with the basal ganglia and its subregions, which play a strong role in selecting and initiating motor behaviors (Alexander and Crutcher 1990). Basal ganglia abnormalities are often observed in patients with OCD and phenomenologically similar disorders, including PANDAS (Giedd et al. 2000) and Tourette's disorder (Mink 2001). In adults with OCD, reduced striatal volumes have been observed in some studies but not others (Aylward et al. 1996; Rotge et al. 2009).

OCD-related hypermetabolism has also been found in the ACC, which plays a major role in error detection as well as the assessment and regulation of emotional information (Diler et al. 2004). This elevated activity may relate to the "not just right" feeling endorsed by many individuals with OCD (Aouizerate et al. 2004). OCD is also associated with increases in the volume of the thalamus, a midline structure that serves as a "switchboard" for several brain regions, among other functions (Gilbert et al. 2000; Rotge et al. 2009). In one pediatric OCD study, elevated thalamic volume was normalized following 12 weeks of effective treatment with paroxetine, a selective serotonin reuptake inhibitor (SSRI; Gilbert et al. 2000). These volumetric changes were associated with changes in OCD symptom severity.

Inconsistencies in neuropsychological and neurobiological OCD research may be due to a number of factors, including small sample sizes, insufficiently sensitive tests, or heterogeneity of OCD symptoms (Abramovitch et al. 2012; Milad and Rauch 2012). For example, compulsive hoarding was previously considered a subtype of OCD (APA 1994) but has been reclassified as a distinct OC-spectrum disorder in *DSM-5* (APA 2013). Individuals with hoarding disorder differ from those with OCD in terms of neural activity during some neuropsychological tasks (Tolin et al. 2014) and in several other domains (Frost et al. 2012). Thus, the inclusion of hoarding in previous OCD samples may have masked (or spuriously enhanced) true differences between individuals with OCD and healthy controls.

Genetics

OCD is a strongly heritable disorder, with strong concordance reported in monozygotic twins (Pauls 2010). Stronger familial concordance has been observed for early-onset OCD (before 18 years; more commonly observed in males) than for later-onset OCD (Pauls et al. 1995). Genetic linkage analyses suggest that a locus on chromosome 9 may contribute to OCD genetic vulnerability (Hanna et al. 2002), as may certain polymorphisms in the 5-HT_{2A} promoter gene, which plays a role in regulation of serotonin (Hu et al. 2006). However, other studies have failed to replicate these findings (Pauls 2008). More recently, a genome-wide association study found evidence for enriched methylation of quantitative trait loci (QTLs) in the single-nucleotide polymorphisms (SNPs) that were most associated with OCD (Stewart et al. 2013). Taken together, these findings suggest that OCD is almost certainly the result of multiple genetic and environmental factors and that additional research is needed to elucidate the genetic underpinnings of OCD.

Some sex differences in the genetic diatheses for OCD have been identified. Women with OCD are more likely than men to possess a low activity-related allele of the monoamine oxidase A gene, whereas men are more likely to possess a low activity-related allele of the catechol-O-methyltransferase (COMT) gene (Lochner et al. 2004). Both genes are responsible for degrading a number of neurotransmitters, including serotonin, dopamine, and norepinephrine (Lochner et al. 2004). Additionally, some genetic polymorphisms (e.g., in the 5-HT_{2A} promoter

gene) have been associated with OCD symptoms only in women (Enoch et al. 2001), whereas other polymorphisms (e.g., SLC1A1, a polymorphism of the glutamate transporter gene) have been linked to OCD only in men (Dickel et al. 2006; Arnold et al. 2006).

Diagnosis

Many individuals without OCD report some obsessions or compulsions (Rachman and De Silva 1978; Salkovskis and Harrison 1984); therefore, OCD is diagnosed only when symptoms reach clinically significant levels of interference or distress (APA 2013). A wide variety of screening and diagnostic measures for OCD are available, including self-report measures and semistructured diagnostic interviews. For an in-depth review of assessment measures for OCD, see Feske and Chambless (2000).

In primary care settings, the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PHQ; Spitzer et al. 1999) is often used. The PHQ is a brief self-report measure that screens for OCD as well as several mood, anxiety, and substance use disorders. It shows fair-to-good reliability with diagnoses assigned by mental health professionals (Spitzer et al. 1999). There are also several OCD-specific self-report measures that can be used with adults and older adolescents. The revised versions of the Obsessive-Compulsive Inventory (OCI-R; Foa et al. 2002) and Padua Inventory (PI-R; Burns et al. 1996) contain symptom-specific subscales and have generally strong psychometric properties. Feske and Chambless (2000) note that the PI-R can be particularly useful for assessing treatment outcome.

Some of the most common clinical interviews for diagnosing OCD in adults are the Anxiety Disorders Interview Schedule-IV (ADIS-IV; Brown et al. 1994) and the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First et al. 1996). These measures assess DSM-IV criteria for OCD; the ADIS-IV in particular provides information regarding the type and severity of obsessions and compulsions, including their frequency and persistence (Di Nardo et al. 1994).

A more precise OCD severity rating can be obtained using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS; Goodman et al. 1989). The Y-BOCS is a gold standard semistructured interview that assesses current and lifetime presence of 36 types of obsessions and 23 types of compulsions. The Y-BOCS provides ratings for severity, time spent, interference, distress, resistance, and perceived control for the individual's primary obsessions and compulsions (Goodman et al. 1989). Administration of the Y-BOCS is generally preceded by assessment with the Y-BOCS Checklist (Steketee et al. 1996), which can be self- or clinician-administered. On the checklist, participants note the absence or presence of 58 obsessions and compulsions, identify the three main obsessions and compulsions, and rate the time spent, interference, distress, resistance, and control for each on a Likert scale (Steketee et al. 1996).

When screening for OCD in younger children, an interviewer may phrase typical assessment questions more simply; for example, "do you do things over and over or

have habits you can't stop?" (Geller et al. 2012, p. 102). The parent-report Child Behavior Checklist (Achenbach 1991) shows good sensitivity and specificity in screening for pediatric OCD (Nelson et al. 2001).

Some of the most widely used clinician-administered measures for diagnosing and evaluating OCD in pediatric samples include the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS; Kaufman et al. 1997) and the Children's Y-BOCS (CY-BOCS, Scahill et al. 1997). The K-SADS covers a broad range of psychiatric disorders, including psychotic and externalizing disorders (see Lewin and Piacentini 2010 for a review). The CY-BOCS is generally considered to be the gold standard interview for assessing OCD in pediatric samples (Lewin and Piacentini 2010). The CY-BOCS is structured similar to the adult Y-BOCS and assesses the presence, frequency, interference, distress, resistance, and perceived control of obsessions and compulsions (Scahill et al. 1997). The symptom checklist of the Children's Y-BOCS (CY-BOCS; Scahill et al. 1997) can also be particularly informative when administered to both parents and children (Geller et al. 2012).

Evaluation

When evaluating OCD, several considerations are warranted. Independent of gender, individuals with OCD may be reluctant to describe their symptoms in detail. This hesitation may occur because the obsessions are embarrassing, alarming, or upsetting to the patient (e.g., in the case of sexual obsessions); because of the belief that describing the symptoms may cause the negative consequences that the person is trying to avoid via compulsions (a phenomenon called thought-action fusion, wherein the individual believes that having a thought is equivalent to acting on the thought; Shafran et al. 1996); or for fear that the patient will be misperceived as dangerous (e.g., in the case of harm obsessions) or psychotic.

In our clinical experience, underreporting is a particular risk for sexual and harm obsessions, often because of shame and fears of being misinterpreted or viewed as potentially dangerous. In the case of sexual obsessions, this apprehension may be increased when the interviewer is of a different gender than the patient (e.g., a male patient and a female interviewer). Therefore, it is important for the interviewer to normalize these symptoms. For example, an interviewer might state that individuals with OCD often experience unwanted, socially undesirable obsessions, such as obsessions related to harming oneself or someone else, of being a pedophile, of being gay, or of harming one's child. Such normalizing statements often make patients more comfortable describing their symptoms and can increase "buy-in" for the treatment.

Independent of gender, it is critical to evaluate insight in patients with OCD. Most individuals with OCD recognize that their symptoms are unreasonable, unnecessary, or take up more time than is warranted (APA 2013). However, a subset of individuals truly believe that their compulsions are necessary and appropriate. These individuals, who can be assigned the diagnostic specifier "with poor insight," show poorer treatment response (Ravi Kishore et al. 2004) and may require different or additional interventions (e.g., adjunctive antipsychotic pharmacotherapy; Ravi Kishore et al. 2004).

The Brown Assessment of Beliefs Scale (BABS; Eisen et al. 1998) is a relatively brief, well-validated, clinician-administered measure that assesses patients' insight into their symptoms (Eisen et al. 1998). When possible, formal assessment with the BABS or a similar standardized assessment method (e.g., item 11 from the Yale-Brown Obsessive-Compulsive Scale; Y-BOCS; Goodman et al. 1989) is advisable.

Differential Diagnosis

OCD shares many clinical features with other emotional disorders. Individuals with body dysmorphic disorder (BDD) also report intrusive thoughts and engage in compulsive behaviors in an attempt to reduce the resulting anxiety. However, in BDD, individuals' obsessions and compulsions are limited to concerns related to physical appearance (APA 2013). If obsessions and compulsions are limited to concerns about weight or body shape, an eating disorder diagnosis should also be considered (APA 2013). While impulse control disorders (e.g., kleptomania) are characterized by behaviors that may be described as "compulsive," these disorders can be distinguished from OCD by the absence of egodystonic obsessions (APA 2013). Furthermore, the compulsive behaviors associated with these disorders are frequently egosyntonic, and the distress experienced by the individual results from the consequences of their compulsive behavior, rather than the behaviors themselves (Dell'Osso et al. 2006).

Hoarding disorder is characterized by persistent difficulty discarding possessions due to a perceived need to save items, distress associated with discarding items, and problematic accumulation of possessions. In contrast to OCD, hoarding disorder is more likely to be egosyntonic and characterized by an absence of attempts to resist hoarding (Frost et al. 2012; Mataix-Cols et al. 2010).

Both mood and anxiety disorders may also be characterized by the experience of repetitive or intrusive thoughts. Of the anxiety disorders, generalized anxiety disorder (GAD) is most phenomenologically similar to OCD (Steketee and Barlow 2002). GAD can be distinguished from OCD by the nature of the repetitive thoughts. In GAD, intrusive thoughts are characterized by excessive anxiety and worry about real-life concerns. In OCD, intrusive thoughts often have odd, irrational, or "magical" content (APA 2013). GAD can also be distinguished from OCD by the absence of compulsions. Additionally, while individuals with major depressive disorder (MDD) may experience intrusive rumination, these thoughts are usually mood-congruent and somewhat egosyntonic. MDD can also be distinguished from OCD by the absence of compulsions (APA 2013).

OCD can be distinguished from psychotic disorders by the absence of other characteristic features of these disorders, such as hallucinations and a formal thought disorder (APA 2013). However, OCD can be characterized by delusional beliefs (O'Dwyer and Marks 2000); these can be diagnosed using the "no insight" specifier in DSM-5.

Finally, despite the similarity in name, most individuals with OCD do not meet criteria for comorbid obsessive-compulsive personality disorder (OCPD; Steketee

et al. 2001). Unlike OCD, which is characterized by intrusive thoughts and repetitive behaviors, OCPD is often characterized by rigidity and egosyntonic preoccupation with orderliness, perfectionism, and control (APA 2013). Individuals exhibiting both obsessions/compulsions and pervasive, maladaptive perfectionism, and rigidity may be diagnosed with both OCD and comorbid OCPD (Coles et al. 2008).

Pharmacotherapy

Meta-analyses suggest a significant benefit from several forms of pharmacotherapy for OCD, with relatively few studies noting sex or gender differences in treatment response. The most widely investigated pharmacological treatments for OCD include clomipramine, a tricyclic antidepressant, and selective serotonin reuptake inhibitors (SSRIs; Soomro, Altman, Rajagopal, & Oakley Browne, 2008). Other biological interventions, which are typically used as an adjunct to conventional treatment or in the case of treatment-resistant OCD, include atypical antipsychotics, deep brain stimulation, transcranial magnetic stimulation (TMS), and D-cycloserine, among others.

Clomipramine, which inhibits the reuptake of serotonin and norepinephrine, was the first drug approved by the Food and Drug Administration (FDA) for the treatment of OCD. Several meta-analyses demonstrate that clomipramine is more effective than placebo in both adults (Ackerman & Greenland, 2002; Greist et al. 1995) and children (Watson and Rees 2008). Importantly, clomipramine can produce undesirable side effects, including dizziness, blurred vision, sedation, constipation, and weight gain. This problematic side effect profile has favored the increased use of SSRIs as a treatment for OCD.

SSRIs produce a clinically significant response in about 40–60 % of OCD patients (Jenike 2004). SSRIs are more effective than placebo even at low doses, but higher doses (e.g., 60–80 mg of fluoxetine and its equivalents) produce greater reductions in symptoms (Bloch et al. 2010). A Cochrane review comparing different types of SSRIs (fluoxetine, fluvoxamine, sertraline, paroxetine, and citalopram) found no significant differences in the effectiveness of each medication (Soomro et al. 2008). Side effects of SSRIs can include dizziness, weight gain, decreased libido and anorgasmia, drowsiness, and insomnia; these and other side effects can be particularly pronounced at the higher doses required to treat OCD.

Randomized controlled trials and meta-analyses that have compared clomipramine and SSRIs have produced mixed results. Some meta-analyses suggest that clomipramine produces larger reductions in symptoms compared to SSRIs in both adults and children (Greist et al. 1995; Sánchez-Meca et al. 2014). However, other meta-analyses have found no differences in efficacy between the treatments (Ackerman et al. 2002). Given the lower risk profile and potentially greater tolerability of SSRIs as compared to clomipramine, SSRIs are generally recommended as a first-line psychopharmacological treatment for both adults (Decloedt and Stein 2010) and, in severe cases, children (Geller et al. 2012) with OCD.

In one study of gender differences in medication response (Mundo et al. 1999), men were more likely than women to experience a worsening of symptoms following administration of intravenous clomipramine (no patients improved following IV clomipramine administration). Following the IV administration, participants were randomly assigned to receive 10 weeks of standard oral treatment with clomipramine or fluvoxamine. Women were more likely than men to experience a reduction in symptoms with clomipramine (94.1 % of women improved relative to post-IV clomipramine treatment vs. 57.1 % of men); no significant gender differences were found for fluvoxamine.

Atypical antipsychotics are sometimes used to augment clomipramine or SSRIs in individuals with treatment-resistant OCD. Risperidone and quetiapine show some promise as adjunctive treatments for treatment-resistant OCD (Fineberg et al. 2006). However, as atypical antipsychotics can cause unpleasant and potentially dangerous side effects, careful consideration is warranted when considering their use (Fineberg et al. 2006).

Several studies have investigated the use of psychotropic medications in postpartum OCD. An open-label trial of fluoxetine for postpartum OCD found that the majority of patients experienced a positive response (Arnold 1999). Another open trial found that augmentation with quetiapine was effective for postpartum women with OCD that had not responded to SSRI or SNRI monotherapy (Misri and Milis 2004). Several case reports suggest that perinatal OCD can be effectively treated with clomipramine (Chelmow and Halfin 1997), fluoxetine (Buttolph and Holland 1990), and various other SSRIs (Sichel et al. 1993).

Importantly, although psychotropic medications are often effective for reducing OCD symptoms, the benefit is often lost when medication is discontinued (Fineberg et al. 2013). Given the short-lived treatment gains and the side effects associated with psychopharmacological treatment, cognitive-behavioral psychotherapy is recommended as a frontline treatment for OCD (NICE 2005; see Psychotherapy below).

In the past decade, advances in neurotherapeutics have highlighted several promising adjunctive and alternative treatments for treatment-resistant OCD. In deep brain stimulation, an electrode is implanted in the brain (typically in the striatum) and electrical impulses are transmitted to interfere with neuronal activity. This approach, although invasive, has been associated with positive short- and long-term results in individuals with chronic, intractable OCD (Greenberg et al. 2006). A newer approach is repetitive TMS (rTMS), wherein a noninvasive handheld device is used to alter magnetic activity in the brain. A recent meta-analysis suggests that rTMS produces a moderate improvement in OCD symptoms compared to placebo or "sham" stimulation (Berlim et al. 2013).

Psychotherapy

Behavioral, cognitive, and combined cognitive-behavioral therapies have demonstrated efficacy in the treatment of OCD. Exposure and response (ritual) prevention (ERP) is a behavioral treatment in which patients are exposed to situations which

normally elicit distress, while compulsions (rituals) are resisted or prevented (Abramowitz 2006; Steketee and Barlow 2002). In contemporary practice, ERP involves "therapist-guided, systematic, repeated, and prolonged exposure to situations that provoke obsessional fear, along with abstinence from compulsive behaviors" (Abramowitz 2006, p. 409). Several meta-analyses have found that ERP produces large and significant reductions in OCD symptoms (Abramowitz 1997; Abramowitz et al. 2002).

Cognitive therapies for OCD focus on identifying and challenging the beliefs that support patients' OCD behaviors and correcting problematic beliefs (Steketee and Barlow 2002; Wilhelm and Steketee 2006). An early meta-analysis of cognitive-behavioral interventions for OCD found that the effect of cognitive interventions was not reliably different from zero, but this null finding was attributed this to the small number of studies directly assessing cognitive interventions (Abramowitz et al. 2002). More recently, a meta-analysis of 16 randomized controlled trials of cognitive-behavioral interventions for OCD found no difference in efficacy between interventions using ERP and those using primarily cognitive interventions; both interventions produced clinically significant reductions in OCD symptoms (Olatunji et al. 2012). Thus, ERP has been classified as a "well-established treatment" for OCD, while cognitive therapy has been classified as a "probably efficacious treatment" (Chambless et al. 1998; DeRubeis and Crits-Cristoph 1998). ERP is generally considered the first-line treatment for adults (NICE 2005) and children (Geller et al. 2012) with OCD. In the case of severe, treatment-refractory pediatric OCD, concurrent psychopharmacological treatment with SSRIs is also recommended (Geller et al. 2012).

D-cycloserine (DCS), an antibiotic that operates on a specific glutamate receptor, has been used to augment CBT for OCD and several anxiety disorders. Preliminary evidence suggests that, although DCS does not appear to alter long-term outcomes, it may reduce the number of sessions required for successful extinction learning and, correspondingly, symptom reduction (Abramowitz et al. 2009; Wilhelm et al. 2008).

Surprisingly, we found only a single study that directly investigated gender differences in treatment response for OCD, although a number of studies have examined gender as a moderator of treatment response. In a study of predictors of response to intense residential treatment for individuals with severe OCD, Stewart and colleagues (2006) found that men were significantly less likely to be classified as treatment responders than women. A meta-analysis of 16 studies of CBT for OCD found that the percentage of females in each study was not significantly associated with effect size (Olatunji et al. 2012). As psychotherapy outcome studies are often underpowered to detect gender differences in treatment response, it is currently unclear whether there are gender differences in the efficacy of ERP for OCD.

Although few studies have investigated treatments specific to perinatal populations with OCD, there is no theoretical basis to believe that OCD in perinatal samples should respond differently to established treatments for OCD (Abramowitz et al. 2003a). In the only existing randomized controlled trial in this population, Timpano and colleagues (2011) found that a cognitive-behavioral prevention

program for pregnant women at risk for OCD resulted in significant reductions in obsessions and compulsions during the first 6 months postpartum. Case studies have also demonstrated successful treatment of perinatal OCD with CBT, either as a stand-alone treatment (Christian and Storch 2009) or with adjunctive pharmacotherapy (Flosnik and Khin 2012).

Several studies and meta-analyses have evaluated the utility of combined treatment (i.e., ERP plus pharmacotherapy) for OCD. A recent meta-analysis suggests that ERP alone is as effective as ERP plus pharmacotherapy for the treatment of pediatric OCD; both approaches were superior to pharmacotherapy alone (Sánchez-Meca et al. 2014). In adults, a meta-analysis of four studies comparing combined ERP and serotonergic pharmacotherapy to pharmacotherapy alone suggested a small but significant benefit of combined treatment over ERP alone, while ERP alone and combined treatment were both superior to pharmacotherapy alone (Tolin 2012). These results suggest that, when available, ERP should be the frontline treatment for OCD, but that the addition of SSRIs or other serotonergic medications may also be of some benefit.

Conclusions

A small but growing body of research suggests several differences in the prevalence, clinical features, and genetic underpinnings of OCD. In pediatric samples, OCD is twice as common in males than females, corresponding to an earlier age of onset in males than females. In adult community samples, the gender distribution is roughly equal, whereas treatment-seeking samples are characterized by a slightly higher percentage of women. Phenomenologically, women are more likely than men to report cleaning and contamination obsessions, particularly in the context of perinatal OCD, whereas men are more likely to report sexual and symmetry-related obsessions. Patterns of comorbidity correspond to commonly observed gender differences in other disorders; for example, men with OCD are more likely to experience comorbid substance-related disorders, whereas women more commonly experience comorbid mood and anxiety disorders. Corresponding to these epidemiological and phenomenological differences, genetic research hints at sex differences in the genetic underpinnings of OCD. Few gender-related differences in OCD treatment responsivity have been identified. As such, cognitive-behavioral therapy and pharmacotherapy with SSRIs are considered frontline treatments for OCD irrespective of gender.

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Obsessive-Compulsive Related Disorders

Elsie Breet and Christine Lochner

Background

Significant advances have been made in characterizing the phenomenology and psychobiology of obsessive-compulsive disorder (OCD) and OCD related disorders (OCRDs) in recent years. It has become increasingly evident that these conditions are not homogeneous entities. Indeed, it has been argued that the heterogeneity typical of OCRDs and related disorders has possibly confounded clinical and biological investigation and may explain some of the inconsistencies across studies.

There is increasing recognition of the role that gender plays in the heterogeneity of these conditions. For example, in OCD, the literature supports a role for gender in obsessive-compulsive symptomatology, comorbidity patterns, genetics, and course of the illness (Lochner and Stein 2003) (covered in Chap. 4). Thus, we undertook a review of the literature on the other OCRDs as categorized in DSM-5 (i.e. body dysmorphic disorder [BDD], hoarding disorder, trichotillomania (hair-pulling disorder) [HPD], and excoriation (skin picking) disorder [SPD]) with a specific focus on gender. In this chapter, each of these conditions will be discussed focusing on phenomenology, psychobiology, pharmacotherapy, and psychotherapy, with special reference to the effects of gender in each section.

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Body Dysmorphic Disorder (BDD)

Diagnosis

BDD is characterized by a preoccupation with barely perceptible or imagined flaws or defaults about physical appearance that the person may believe is deformed or unattractive (American Psychiatric Association (APA) 2013). Although the word 'preoccupation' is not operationalized in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (APA 2013), it is understood to mean that thoughts of the perceived defect should last for at least an hour or longer per day (Phillips 2009). These preoccupations can focus on any body part, such as skin (e.g. wrinkles), hair (e.g. excessive body hair), and nose (e.g. size) (Phillips and Kaye 2007). Among adolescent samples, preoccupations have been found to focus mainly on skin, hair, and stomach (Phillips et al. 2006a).

BDD differs from normal appearance concerns in that BDD is associated with excessive preoccupations and consequent behaviours related to the person's appearance (e.g. mirror-checking, asking for reassurance) that are time-consuming, difficult to control/resist and that cause significant distress or impairment in functioning (APA 2013). Level of insight may vary; the specifiers used to describe insight regarding beliefs about appearance are good/fair, poor, and delusional/absent. The poor insight specifier is most commonly used in BDD (Vargel and Ulusahin 2001).

Males and females generally present with similar body dysmorphic symptomatology, however, muscle dysmorphia is a form of BDD that occurs almost exclusively in males and is described as a preoccupation that one's body is too small, 'puny', and inadequately muscular (Pope et al. 2000).

Epidemiology

BDD is a relatively common disorder, affecting 0.7–2.4 % of the general population (Faravelli et al. 1997; Koran et al. 2008; Otto et al. 2001; Rief et al. 2006). Gender distribution appears to be equal across the globe; for example, 2.2 % of males and 2.5 % of females in the USA (Koran et al. 2008); and 1.4 % of males and 1.9 % of females in Germany (Buhlmann et al. 2010; Koran et al. 2008). The prevalence rate of BDD differs across settings; however, studies in clinical samples report a prevalence of 9–12 % among dermatology patients and 3–53 % among cosmetic surgery patients, 8–37 % among OCD patients, 11–13 % among social anxiety disorder patients, and 26 % among individuals with HPD (Aouizerate et al. 2003; Brawman-Mintzer et al. 1995; Castle et al. 2004; Hollander et al. 1993; Ishigooka et al. 1998; Perugi et al. 1997; Phillips et al. 1996, 2000; Sarwer et al. 1998; Uzun et al. 2003; Vargel and Ulusahin 2001; Vindigni et al. 2002). In adolescent samples, prevalence rates ranging between 6.7 and 14 % in psychiatric inpatient settings (Phillips and Rogers 2011) and 2.2 % in high school settings (Mayville et al. 1999) have been reported. Gender distribution within these contexts is not, however, always reported.

Developmental Course

BDD usually begins during adolescence and follows a chronic course if not treated (Phillips et al. 2005; Phillips and Diaz 1997). Regarding gender differences, some studies report that females demonstrate a slightly higher prevalence and earlier symptom onset of BDD compared to males, while other studies suggested that there are more similarities than differences between males and females with BDD (Phillips and Diaz 1997; Phillips et al. 2006b). In one study, males with BDD were significantly older, more likely than females to be obsessed with their genitals, body build, and thinning hair/balding, excessive weight lifting, and to have comorbid substance use disorders (Phillips et al. 2006b). On the other hand, females were more likely than males to obsess about their skin, stomach, weight, breasts/chest, buttocks, thighs, legs, hips, toes, and excessive body/facial hair, while also being excessively concerned with more body areas compared to males (Phillips et al. 2006b). Females also reported performing more repetitive and safety behaviours, and were more likely to use camouflaging techniques, check mirrors, change their clothes, pick their skin, and have comorbid eating disorders (Phillips et al. 2006b). BDD may occur in older individuals although not many studies have included an older age group and with some reporting a decrease in the prevalence of BDD after the age of 44 years (Koran et al. 2008). The clinical features of BDD in adolescents and adulthood share many similarities. Differences include higher reported rates of delusional BDD beliefs and lifetime rates of suicide attempts among adolescents when compared with adults (Phillips et al. 2006a).

Psychobiology

Genetics

In two different samples, Phillips and colleagues found that between 5.8 and 6.4 % of first-degree relatives of BDD probands had BDD (Phillips et al. 2005). There also is some evidence to suggest a familial link with OCD (Bienvenu et al. 2000). However, further genetic investigation is needed in order to identify candidate genes involved in BDD (Chosak et al. 2008).

Neuroimaging

There have been relatively few neuroimaging studies have of BDD. An early SPECT study suggested that changes in frontostriatal and temporoparietaloccipital circuits may play a role in BDD (Carey et al. 2004). A more recent fMRI study concluded that abnormalities in visual processing and frontostriatal systems may be associated with the BDD (Feusner et al. 2010). A study of brain morphology reports significantly smaller mean volumes of orbitofrontal cortex and anterior cingulate cortex in individuals with BDD when compared to healthy controls (Atmaca et al. 2010).

Further work is needed to determine whether genetic and neuroimaging findings differ by sex in BDD.

Evaluation

Assessment

There are a number of measures that may be used to assess BDD. These include the *Yale-Brown Obsessive Compulsive Scale Modified for Body Dysmorphic Disorder (BDD-YBOCS)* (Phillips et al. 1997), the *Body Dysmorphic Disorder Examination (BDDE)* (Rosen and Reiter 1996), and the *Psychiatric Status Rating Scale for Body Dysmorphic Disorder (BDD-PSR)* (Phillips et al. 2006b). Insight into the excessiveness or irrationality of symptoms can be assessed with the *Brown Assessment of Belief Scale (BABS)* (Eisen et al. 1998). Although these measures can be used to assess BDD in both males and females, there may be sex differences across the scales. For example, in a study of 200 participants in the USA, the BDDE reported more severe BDD among females, whereas in the same sample, the BDD-PSR reported more severe BDD among males compared to females (Phillips et al. 2006b).

Differential Diagnosis

BDD shares many clinical features with other psychiatric disorders. If concerns are focused on being fat, an eating disorder should be diagnosed instead of BDD (APA 2013). In BDD, the preoccupations and repetitive behaviours are concerned with appearance; this is not the focus of obsessions and compulsions found in other obsessive-compulsive and related disorders. For example, if any form of hair removal (e.g. plucking or pulling) is done in order to improve a perceived flaw or impairment in facial appearance, BDD should be diagnosed and not HPD (APA 2013). Illness anxiety disorder is distinguished from BDD in that BDD is not preoccupied with having or acquiring any serious illness (APA 2013). Depression is differentiated from BDD because in BDD preoccupations and repetitive behaviours are focused on appearance (APA 2013). Although anxiety disorders are common in BDD, the social anxiety or avoidance in BDD is due to perceived appearance-related defects or fear that others may reject or ridicule the patient because of perceived flaws or defects (APA 2013). BDD is distinguished from psychotic disorders in that the deletions are related to appearance and other psychotic symptoms (e.g. disorganized behaviour) are absent (APA 2013).

Psychotherapy

Cognitive-behavioural therapy (CBT) that specifically targets BDD symptoms is currently considered first-line psychotherapy for this condition (Phillips and Rogers 2011). Similar to OCD, CBT for BDD primarily consists of cognitive restructuring (to change the assumptions and beliefs of the perceived flaw) and exposure and response prevention (ERP) (Gupta et al. 2013). These cognitive-behavioural strategies are aimed at changing maladaptive beliefs and perceived defaults/flaws, and in doing so, placing less focus on the minor details of physical appearance (Gupta et al. 2013). The ERP part of therapy entails revealing a perceived defect in social

situations (e.g. in a shopping mall) without the usual 'cover up' rituals (e.g. wearing excessive make-up to cover it). CBT consisting of cognitive restructuring and ERP has been used effectively to decrease preoccupation and time spent on repetitive behaviours in BDD (McKay et al. 1997). Additional strategies – such as perceptual retraining with mirrors, or habit reversal for BDD-related skin picking – may also be used (Phillips and Rogers 2011). Notably, intensive engagement and ongoing motivational interventions are often needed when treating BDD patients as many of these patients have poor or absent insight (Phillips et al. 2010; Phillips and Rogers 2011). Although BDD-specific CBT has been used to effectively treat this disorder among adolescents, there is a paucity of work investigating whether and how these techniques have been adapted and tested in this age group (Phillips and Rogers 2011). No sex differences have been reported in response to psychotherapy BDD.

Pharmacotherapy

In BDD, SRIs such as clomipramine, fluvoxamine, fluoxetine and citalopram have all shown efficacy or partial efficacy (Allen and Hollander 2000). There are preliminary data (Allen et al. 2008); Phillips et al. 1996) that suggest that serotonin-norepinephrine reuptake inhibitors such as venlafaxine may also be efficacious for BDD. Currently, it is recommended that SSRIs should be used for at least 12 weeks and should be taken at higher doses for the optimal therapeutic effect (Phillips and Hollander 2008). Antipsychotics, benzodiazepines, lithium, antiepileptics, and monoamine oxidase inhibitors (MAOIs) have also been used to treat BDD with varied success (Gupta et al. 2013). Although the research is limited, SRIs are more effective when compared to non-SRI antidepressants or other types of psychotropic medication (Phillips and Hollander 2008). In children and adolescents, SRIs have also shown clinically significant improvement in BDD symptoms (Albertini et al. 1996; Phillips et al. 1995). However, caution is necessary when treating patients in this age group given concerns about suicidality and SRI use in adolescents (Phillips and Rogers 2011). If successful, SRI treatment may result in less frequent and intense appearance preoccupations, decreased BDD-related stress, and less intense urges and less time spent performing compulsive/safety behaviours (Phillips and Hollander 2008). Anecdotally, some patients with BDD may obtain added benefit from the combination of an SRI and CBT, but there are no systematic comparisons of pharmacotherapy, psychotherapy, and their combination. No studies report sex differences with regard to treatment outcomes in response to pharmacotherapy in BDD.

Hoarding Disorder

Diagnosis

The core feature of hoarding disorder is persistent difficulty discarding or parting with possessions regardless of their actual value (APA 2013). Here, the word

'persistent' refers to a long-standing difficulty rather than a temporary situation/event (e.g. inheriting property) that results in excessive clutter. The difficulty associated with discarding possessions may be related to sentimental significance, beliefs that the item may be needed in the future, that getting rid of the possession may be wasteful (Gilliam and Tolin 2010), or to aesthetic issues (Frost et al. 2011b). Use of the word 'discarding' in DSM suggests that the difficulty experienced by the individual with hoarding disorder is not only limited to the act of throwing away of possessions but also includes any attempt to sell, give away, or recycle possessions (Frost et al. 2011b). Since children are often not in control of their living environment and discarding behaviour it may be necessary to consider adapting some of the criteria (e.g. Criterion C) used to diagnose hoarding disorder (Plimpton et al. 2009). The items saved by people who hoard are not necessarily limited to worthless or worn-out things but may also include things that are new (Frost et al. 2011b). Commonly saved items are magazines or newspapers, books, notes, and clothes (Frost and Gross 1993; Frost and Hartl 1996).

Individuals with hoarding disorder *purposefully* save possessions or are reluctant to discard items, so the saving behaviour is not passive or merely due to messiness/laziness (Frost et al. 2011b). Disorganized clutter is the hallmark consequence of hoarding disorder and results in an area becoming so cluttered or filled up that it is nearly impossible to use the space for its intended use or to find important items among the clutter (Tollin et al. 2008b). For example, the individual who hoards may not be able to sleep in the bed, sit in a chair, or eat at the table due to the clutter. These spaces usually refer to living areas of the home (e.g. kitchen) rather than to areas of the home that are commonly used for storage (e.g. garage) (Saxena and Maidment 2004).

Pathological hoarding results in clinically significant distress or impairment in functioning. For example, utilities such as water or electricity may be cut off (Kim et al. 2001), health may be compromised due to unsanitary living conditions (Frost et al. 2000), or relationships may deteriorate due to the hoarding (Tolin et al. 2008b).

In addition to the diagnostic criteria, DSM-5 also includes a specifier for excessive acquisition. Individuals with hoarding disorder may exhibit excessive acquisition behaviour in the form of compulsive buying, excessive acquiring of free items (Frost et al. 2001; Frost et al. 2009), and stealing (Nordsletten et al. 2013). Insight into the hoarding behaviour and its implications may vary, and DSM-5 has included a specifier to indicate good/fair, poor, or absent insight/delusional beliefs. Generally, patients with hoarding disorder demonstrate poor insight (Frost and Hartl 1996; Matsunaga et al. 2010) necessitating that family and friends report the case to the relevant authorities or seek help (Tolin et al. 2010a).

The phenomenology of hoarding disorder does not differ significantly between males and females. Therefore, DSM-5 criteria are equally suitable for both sexes (Mataix-Cols et al. 2010). There is a paucity of studies on gender differences in comorbidity patterns among individuals with hoarding disorder. Nevertheless, in one study, it was found that in adults with hoarding disorder, males with hoarding disorder were more likely than females to meet the diagnostic criteria for OCD (Frost et al. 2011a). In children with OCD, more girls compared to boys report symptoms of hoarding (Mataix-Cols et al. 2008).

Epidemiology

The point prevalence of clinically significant hoarding among community samples in the USA and Europe ranges from 2 to 5 % (Iervolino et al. 2009; Mueller et al. 2009; Samuels et al. 2008). It is possible that the prevalence of hoarding increases with age because compulsive hoarding is a chronic and progressive disorder (Grisham and Norberg 2010). Certainly, older individuals are more likely than children/adults to report clinically significant symptoms of hoarding disorder (Samuels et al. 2008). Notably, one study reported that hoarding was almost three times more prevalent in individuals over the age of 54 years when compared to younger individuals aged 34–44 years (Samuels et al. 2008).

Research findings have yielded mixed results with regard to sex differences in the prevalence of hoarding disorder. Two epidemiological studies reported that adult males were twice as likely to report symptoms related to hoarding (Iervolino et al. 2009; Samuels et al. 2008) than females. In adolescence, prevalence rates of 2 % have been reported with higher rates among girls than boys (Ivanov et al. 2013).

Development Course

Hoarding disorder generally develops during childhood or adolescence (Grisham et al. 2006), usually between 11 and 15 years (Ayers et al. 2010), although age of onset can be as young as 4 years (Ayers et al. 2010; Plimpton et al. 2009). One study found that 60 % of participants reported having experienced hoarding symptoms before the age of 12 years, while 80 % reported age of onset by the age of 18 years (Grisham et al. 2006). Although the majority of individuals with pathological hoarding experience a gradual increase of these symptoms throughout their lifetime (Samuels et al. 2008), others may develop symptoms related to hoarding disorder after experiencing a stressful life event (Grisham et al. 2006). Hoarding disorder appears to follow a chronic course with few individuals reporting full remission (Pinto et al. 2007). Clinically significant problems of hoarding are more frequently reported among older (mean age 50 years) compared to younger individuals (Pertusa et al. 2008; Samuels et al. 2008).

Evaluation

Assessment

Earlier measures that assessed hoarding did so with the assumption that hoarding was a form of OCD (Frost et al. 2011b); i.e. hoarding obsessions and compulsions have been measured with the Yale–Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al. 1989). More recently, self-report (e.g. Saving Inventory-Revised) (Frost et al. 2004), interview (Hoarding Rating Scale-Interview) (Tolin et al. 2010b), and observational measures (The Clutter Image Rating Scale) (Frost et al. 2008) have been developed to specifically assess hoarding behaviour. Although males and females do not seem to differ in terms of clutter or difficulties discarding items, some

studies have reported sex differences in acquisition (Frost et al. 2011a). For example, in one study, females scored higher than males on the excessive acquisition subscale of the Saving Inventory-Revised (Frost et al. 2004). However, not all data are consistent; one study found that females with hoarding disorder scored higher on the compulsive buying but not the excessive acquisition of free things when assessed with the Compulsive Acquisition Scale (CAS) (Frost et al. 2002).

Psychobiology

Genetic

Many individuals with hoarding disorder report at least one first-degree relative with hoarding symptoms (Pertusa et al. 2008; Samuels et al. 2007; Seedat and Stein 2002). Family studies report that both genetic and non-shared environmental factors account for the variance in symptoms of hoarding (Iervolino et al. 2009). Twin studies have reported a strong phenotypic correlation between excessive acquisition and difficulty discarding, suggesting that there may be a significant genetic overlap in their co-occurrence in hoarding disorder (Nordsletten et al. 2013). Twin studies among adolescents provided support for a genetic influence in the variation of hoarding symptoms among boys but not girls (Ivanov et al. 2013). Rather, shared and non-shared environmental effects explained a significant portion of the variance in hoarding symptoms among girls (Ivanov et al. 2013). Research to investigate candidate genes for hoarding disorder is still in its infancy, and there are no known studies reporting sex difference in this regard.

Neuroimaging

Compared to individuals with OCD with hoarding symptoms, individuals with hoarding disorder show abnormal activity in the frontal cortical regions and the anterior cingulate cortex (ACC) (e.g. areas which are involved in executive functioning such as decision-making) (Krain et al. 2006; van Veen and Carter 2002), prefrontal cortex (Tolin et al. 2009), and the temporal regions (involved in memory) (Read 1981). In a study to examine the neural mechanisms of impaired decision-making in hoarding disorder, the authors concluded that biphasic abnormality in ACC and insula function was associated with problems in identifying the emotional significance of a stimulus, generating appropriate emotional responses, or regulating affective state during decision-making (Tolin et al. 2012). Functional magnetic resonance imaging in a sample of OCD participants in which some met the criteria for hoarding disorder suggested that participants with comorbid hoarding disorder have increased activity in the left lateral OFC and parahippocampal gyrus when compared to participants with only OCD (Tolin et al. 2009). These neuroimaging studies did not report on sex differences.

Neuropsychological Testing

Neuropsychological testing has shown deficits in attention (Grisham et al. 2007), organization, decision-making/planning (Lawrence et al. 2006), and memory (Hartl

et al. 2004) among individuals with pathological hoarding. A study that investigated executive functioning in older individuals with hoarding disorder suggested significant dysfunction in certain areas (e.g. mental control, inhibition, working memory, and set shifting) compared to healthy controls, and this impairment was associated with increased symptom severity (Ayers et al. 2013). To our knowledge, there is currently no literature on differences between males and females in terms of neuropsychological functioning in HD.

Differential Diagnosis

Hoarding disorder is not diagnosed if the symptoms are related to a medical condition (e.g. brain lesions in the anterior ventromedial prefrontal and cingulate cortices following injury) (Anderson et al. 2005). A distinction should be made between symptoms related to hoarding disorder, neurodevelopmental disorders (Ivanov et al. 2013), or neurodegenerative disorders like Alzheimer's disease. A diagnosis of hoarding disorder should not be made if the accumulation of items is due to delusions or symptoms related to schizophrenia spectrum or psychotic disorders (APA 2013). The accumulation of items may also be due to psychomotor retardation, fatigue, or loss of energy during a major depressive episode in which case hoarding disorder should not be diagnosed (APA 2013). In OCD, the hoarding behaviour is usually unwanted and distressing (APA 2013). Moreover, excessive acquisition is generally not present in OCD, but if it does occur, the behaviour is usually related to a specific obsession (e.g. buying items that have been accidentally touched in order to avoid contamination of others) (Mataix-Cols et al. 2010). Individuals who exhibit hoarding behaviour that is related to OCD are more likely to accumulate bizarre items (e.g. such as rotten food or bodily products) (Mataix-Cols et al. 2010).

Psychotherapy

Since CBT used to treat OCD has not yielded effective treatment outcomes in individuals with hoarding disorder (Frost and Tolin 2008; Steketee and Frost 2003, 2007), a CBT model adjusted for compulsive hoarding was developed. This model targets motivational concerns, improving information-processing deficits, cognitive reconstruction of beliefs about and attachment to possessions, and behavioural avoidance that is maintaining hoarding symptoms (Gilliam and Tolin 2010). In addition to ERP, CBT for hoarding disorder also includes excavation of saved material and decision-making training (Saxena and Maidment 2004). Compulsive hoarding has been treated successfully with this particular CBT model of hoarding (Frost 2010) with no apparent sex differences in outcome. The combination of CBT and pharmacotherapy may anecdotally be useful in the treatment of hoarding disorder (Saxena 2011).

Pharmacotherapy

There is preliminary evidence that some of the SRIs, e.g. paroxetine, or other medications like the serotonin-norepinephrine reuptake inhibitor venlafaxine may be effective in the treatment of hoarding disorder (Saxena 2011). It is not known, however, whether males and females with hoarding disorder differ with regard to their response to these medications.

Trichotillomania (Hair-Pulling Disorder)

Diagnosis

In DSM-5, a key diagnostic criterion for trichotillomania (hair-pulling disorder or HPD) is the recurrent pulling of one's own hair, resulting in hair loss (APA 2013). Hair-pulling may occur anywhere on the body where hair grows, the most common areas being the scalp, eyebrows, and eyelashes (Papadopoulos et al. 2003; Reeve et al. 1992; Stanley et al. 1994). Although hair-pulling may be localized and visible, it may also be distributed across different areas in order to make the hair-pulling less noticeable (Stein et al. 2010). Males are more likely than females to pull hair from a variety of areas, and more frequently pull hair from the face, chest, and abdomen (Christenson et al. 1994). Hair-pulling behaviour may occur for brief periods, prolonged episodes, or occur dozens of times a day for seconds or minutes at a time (Walsh and McDougle 2001). Individuals who meet the diagnostic criteria for HPD make repeated attempts to decrease or stop the hair-pulling (Lochner et al. 2012b; APA 2013). Some barriers that may be used to decrease or stop hair-pulling include wearing hats/mittens, or alternative activities (e.g. sitting on hands) (Walsh and McDougle 2001). Pathological hair-pulling may cause clinically significant distress in several areas (e.g. social, occupational, or academic) of the individual's life (APA 2013). For example, HPD has been found to be associated with impaired social functioning, lowered career aspirations, missed work days, (Diefenbach et al. 2005; Seedat and Stein 1998; Woods et al. 2006), and family rupture (Moore et al. 2009).

Epidemiology

Earlier research considered HPD to be a rare disorder; however, today it is considered to be much more common. Slight discrepancies across prevalence studies may be due to methodological issues (e.g. different definitions used) and cultural norms (e.g. hair loss may be more acceptable among males than females) (Duke et al. 2010). Large-scale epidemiological studies are needed to establish prevalence rates of HPD among different age groups.

HPD is more frequently noted in females than males. A study of college students reported a life time prevalence of 0.6–3.4 % in females and 0.6–1.5 % in males (Christenson et al. 1991). One study in children with HPD reported a female-to-male ratio of 2.5:1 (Oranje et al. 1986). Similarly, an adult sample showed a

female-to-male ratio of 2:1 (King et al. 1995). During toddlerhood through to early childhood, there appears to be approximately equal reported rates of HPD between males and females, while in late childhood through to adulthood more females compared to males report HPD (Labouliere and Storch 2012).

Developmental Course

HPD demonstrates a bimodal symptom onset, occurring either in infancy or in adolescence (Swedo and Rapoport 1991). The mean age of onset for adult HPD is 13 years with a later age onset considered to be associated with more severe symptoms, greater treatment resistance, and a higher likelihood of comorbidity with other mental disorders (Swedo et al. 1992; Winchel 1992). The symptom severity of HPD tends to increase through adolescence, peaking from the age of 16 to 18 years, and decreasing in severity with age (Flessner et al. 2008b).

Psychobiology

The specific causes of HPD have not yet been established. Multiple independent or interdependent pathways that may be biological, psychological, or social may be relevant (Diefenbach et al. 2000). For example, an individual with a genetic vulnerability to emotional dysregulation through biological processes may develop hair-pulling behaviour triggered by a traumatizing or stressful life event (i.e. hair-pulling to reduce anxiety) (Duke et al. 2010).

Genetic

A twin study to investigate differences in HPD rates among monozygotic and dizygotic twin pairs provided some evidence for the heritability of HPD (Novak et al. 2009). Mutations on the SLITRK1 genes have been suggested to be implicated in HPD (Zuchner et al. 2006). More recent findings indicate that sapap3 gene variants may play a role in HPD as well as OCD (Hemmings et al. 2011; Zuchner et al. 2009). More research is needed to investigate whether or not sex differences are relevant to these findings.

Neuroimaging

HPD has been associated with reduced neural activity in the left putamen (Chamberlain et al. 2007) and heightened brain metabolism in the cerebellum as well as right superior parietal cortex (Swedo and Rapoport 1991). Positron emission tomography indicated that females with HPD had significantly increased global grey matter and normalized cerebellar as well as right superior parietal glucose metabolic rates when compared to healthy controls (Swedo et al. 1992). More recently, increased grey matter density was found in the left amygdalohippocampal complex, left striatum, and numerous cortical regions among individuals with HPD (Chamberlain et al. 2008). In terms of white matter, more work is needed; findings vary across studies (Chamberlain et al.2010; Roos et al. 2013).

Hormonal System

Early research studies provided some evidence for premenstrual exacerbation of HPD symptoms (Christenson et al. 1992; Keuthen et al. 1997). One study to assess compulsive hair-pulling among a sample of pregnant females reported that in some females pregnancy may be associated with increased symptoms of hair-pulling (Keuthen et al. 1997).

Evaluation

Assessment

HPD assessment should consist of making a diagnosis, developing a functional analysis that informs treatment planning, and determining a baseline symptom severity in order to track treatment progress (Diefenbach et al. 2005). A number of diagnostic interviews and symptom severity measures are available (Duke et al. 2010). For example, self-report measures include the Massachusetts General Hospital Hairpulling Scale (MGH-HPS) to measure hair-pulling severity and urges associated with pulling (Keuthen et al. 1995) and the Milwaukee Inventory for Style of Trichotillomania-Adult Version (MIST-A) to assess automatic and focused trichotillomania subtypes (Flessner et al. 2008c). The Psychiatric Institute Trichotillomania Scale (PITS) is a clinician rating scale used to assess pulling sites, duration, frequency, interference, distress, and severity of hair loss (Stanley et al. 1999). The NIMH Trichotillomania Severity Scale (NIMH-TSS) is a clinical interview used to assess time, resistance, distress, and interference (Goodman et al. 1989). In children, the Trichotillomania Scale for Children (TSC) (Tolin et al. 2008a) may be used to assess distress and severity, while the Milwaukee Inventory for Style of Trichotillomania-Child Version (MIST-C) (Flessner et al. 2007) is used to measure the degree to which children and adolescents engage in focused and automatic hair-pulling.

Differential Diagnosis

HPD is not diagnosed when hair loss/removal is due to normative hair removal/manipulation (e.g. to improve physical appearance), concerns related to other obsessive-compulsive and related disorders (e.g. body dysmorphic disorder) (APA 2013), neurodevelopmental disorders (e.g. tic disorders) (Duke et al. 2010), a psychotic disorder (e.g. delusions that by pulling the hair out is a way of riding oneself from demons) (Franklin and Tolin 2007), or another medical condition (e.g. alopecia areata) (Sah et al. 2008).

Psychotherapy

Various types of behavioural modification approaches are used to treat HPD. Habit-reversal techniques are considered effective in children/adolescents as well as adults (Labouliere and Storch 2012; Ninan et al. 2000). The main components of this treatment modality are self-monitoring pulling behaviours, developing coping strategies

(i.e. addressing situations where pulling occurs and using alternative behaviours to avoid pulling), obtaining social support networks, relaxation therapy, learning competing responses (e.g. clenching fists or sitting on hands) (Sah et al. 2008), and awareness training (e.g. to help the individual become alert to hair-pulling triggers) (Flessner et al. 2008a). During therapy, patients should also be encouraged to learn from relapses rather than considering them to be failures. Some evidence suggests that behavioural therapy is more effective than pharmacotherapy (Flessner et al. 2008a; Ninan et al. 2000). However, the effect of behavioural and cognitive strategies may vary across individuals (Mansueto et al. 1999). There is no evidence to suggest that males and females differ with regard to treatment outcomes with psychotherapy.

Pharmacotherapy

The effectiveness of SSRIs in the treatment of HPD has yielded mixed findings with a number of studies indicating that SSRIs are not efficacious in reducing hair-pulling symptoms among children/adolescents or adults (Franklin et al. 2011; Labouliere and Storch 2012). More recent pharmacotherapy developments suggest that treatment approaches that address non-serotonergic neurotransmitter systems may be effective in reducing pulling behaviour and pulling urges (Franklin et al. 2011). For example, a glutamate modulator (*N*-acetylcysteine [NAC]) (Grant et al. 2009), an opoid antagonist (naltrexone) (De Sousa 2008), and an atypical neuroleptic (olanzapine) (Van Ameringen et al. 2010) have been reported to be effective in treating HPD. There is some evidence that combined treatment of behavioural therapy with pharmacotherapy may be useful (Franklin et al. 2011). No sex differences have been reported with regard to pharmacotherapy in HPD.

Excoriation (Skin Picking) Disorder

Diagnosis

Excoriation (skin-picking) disorder (SPD) is characterized by recurrent picking of skin that leads to tissue damage (Grant et al. 2012a; APA 2013). Individuals may spend a significant portion of each day picking their skin with many reporting that they spend several hours each day engaged in skin picking behaviour (Tucker et al. 2011; Keuthen et al. 2000; Wilhelm et al. 1999). The triggers for skin picking vary and may be associated with the individual's emotional state (e.g. feelings of stress, anxiety, boredom, or anger) or by the feel (e.g. a scab) or appearance (e.g. insect bite) of the skin (Grant et al. 2012a). Generally, individuals will use their fingernails to pick their skin, but an instrument (e.g. tweezers, pins) may also be used (Hayes et al. 2009). Those who engage in skin picking often pick areas on the face, back, neck, or scalp (Arnold et al. 1998; Bohne et al. 2002; Keuthen et al. 2000; Wilhelm et al. 1999). Individuals may initially not be aware that they are picking but become aware of this over a certain period of time, for example, when someone else brings it to their attention (Grant et al. 2007; Keuthen et al. 2000). Individuals with SPD

make repeated attempts to decrease or stop picking their skin (Lochner et al. 2012a; APA 2013). The picking causes significant distress or impairment in social, academic, work, or other areas of functioning (Flessner and Woods 2006; Lochner et al. 2012a). The word *distress* emphasises the negative effects – such as shame and embarrassment – that may be experienced by the individual with SPD (Hayes et al. 2009). Pathological skin picking is more frequently diagnosed in females than males (Grant et al. 2012a; Hayes et al. 2009).

Epidemiology

Prevalence rates for skin picking disorder vary from 1.2 to 5.4 % in student, community, and dermatology samples (Odlaug and Grant 2012). In the general population, a lifetime prevalence of 1.4 % has been estimated (Keuthen et al. 2010). Although SPD is common in both sexes, there is a trend that females are more likely than males to report skin picking (Grant et al. 2012a).

Development Course

The age of onset for SPD varies. The condition may occur in childhood (<10 years old), adolescence (estimated mean age 13–15 years), or later in life (between ages 30 and 45) (Arnold et al. 1998; Calikusu et al. 2003; Keuthen et al. 2000; Odlaug and Grant 2007; Simeon et al. 1997). Clinical studies show that SPD is chronic (Bohne et al. 2005).

Early onset of SPD has been associated with a longer duration of skin picking before seeking treatment, and more frequent non-conscious picking when compared to individuals with late onset SPD (Odlaug and Grant 2007). The same study found no significant difference between early and late onset SPD with regard to symptom severity, comorbidity, and social functioning (Odlaug and Grant 2007a). One study suggested that males with SPD derived more pleasure from skin picking, and picked from areas that were less visible (Calikuşu et al. 2012).

Psychobiology

Neuroimaging

There is a paucity of neuroimaging studies in SPD. A diffusion tensor imaging (DTI) study has, however, indicated that disorganization of the tracts involved in motor generation and suppression is implicated in the pathophysiology of SPD (Grant et al. 2012b).

Neuropsychological Testing

Impaired inhibitory control may be implicated in SPD (Grant and Odlaugh 2009). Response inhibition is dependent on neural circuitry that includes the inferior

frontal gyrus and is affected by the noradrenaline system suggesting that dysregulation in noradrenaline and the inhibitory network may play a role in SPD (Grant and Odlaugh 2009). Sex differences in such inhibitory control have not, however, been reported in SPD.

Evaluation

Assessment

The initial interview should assess clinical characteristics of the skin picking behaviour. Clinical questions are aimed at establishing the time spent picking per day, the portion of the time spent on picking, the triggers for picking behaviour, the areas of the body picked, and whether picking caused medical complications. Individuals with SPD should also be screened for comorbid psychiatric disorders. The individual should also be screened for alcohol and drug use as skin picking may result from the use of cocaine or methamphetamine.

Differential Diagnosis

SPD should be differentiated from psychotic disorders when the picking of skin is due to a delusion or tactile hallucination (i.e. formication) (APA 2013). Discrimination between disorders with compulsive and impulsive features is necessary to distinguish SPD from other OCRDs. For example, when the skin is picked in order to improve appearance, BDD should be diagnosed and not SPD (Grant et al. 2006). Stereotypical movement disorders may be characterized by repetitive self-injurious behaviour, but onset occurs in the early developmental period, e.g. patients with Prader-Willi syndrome exhibit early onset skin picking (Banga and Connor 2012). SPD is not diagnosed when skin lesions are attributable to factitious disorder in which patients act intentionally similar to individuals with skin picking disorder (Hlal et al. 2013). If the skin picking occurs with the intention to harm oneself, non-suicidal self-injury is diagnosed and not SPD (Snorrason et al. 2012).

Psychotherapy

More females than males seek treatment for SPD (Bohne et al. 2005). A variety of psychotherapeutic approaches have been used to treat SPD. Similar to HPD, HRT (Teng et al. 2006) and acceptance-enhanced behavioural therapy (i.e. combination of habit reversal therapy and commitment therapy) (Flessner et al. 2008a) have demonstrated significant reductions in skin picking. Internet-based treatment may also be useful and requires no patient-therapist interaction (Grant and Odlaugh 2009). Picking behaviour in individuals with a neurodevelopmental disorder or disability may require specialized treatment interventions such as use of protective

clothing (e.g. hat, gloves), response interruption and redirection, punishment, and extinction (Lang et al. 2010). There is currently no literature to suggest that males and female respond differently to the different psychotherapeutic modalities.

Pharmacotherapy

SSRIs such as fluoxetine, escitalopram, or citalopram, and opioid receptor antagonists such as naltrexone and NAC may demonstrate benefit for the treatment of SPD (Banga and Connor 2012; Odlaug and Grant 2007b). No sex differences have been reported in terms of therapeutic outcomes to pharmacotherapy.

Conclusion

This chapter covered a review of the literature on the phenomenology, psychobiology, pharmacotherapy, and psychotherapy of OCRDs in DSM-5 with a specific focus on sex. Data have been accumulating on sex differences in prevalence and comorbidity, but there are few data on sex differences in psychobiology or treatment response. Further research is therefore needed to address whether these exist, and if so what the clinical implications are.

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Trauma and Stressor-Related Disorders

Kate Walsh, Jennifer B. Wells, Briana Lurie,
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Introduction

This chapter focuses on gender differences in trauma exposure and the development of posttraumatic sequelae over the life course. First, we review the prevalence of trauma exposure and posttraumatic sequelae with particular attention to comorbidity and disability or impairment. Second, we review psychobiological processes that explain risk for various types of posttraumatic sequelae with a focus on gender and comorbidity. Third, we review the DSM-5 diagnostic criteria for various disorders associated with trauma exposure. Fourth, we review the best available instruments designed to assess these disorders. Fifth, we review the current best practices for treatment of these conditions including psychopharmacology, psychotherapy, and combined approaches designed to treat comorbid conditions. We conclude that despite a large body of research documenting gender differences in trauma exposure and trauma-related disorders much work remains to be done in this area.

Epidemiology

Exposures

Potentially traumatic event (PTE) exposure is common with 60–90 % of adults worldwide reporting exposure to at least one PTE during their lifetime (e.g., Bohnert and Breslau 2011; Kessler et al. 1995; Perkonigg et al. 2000; Resnick et al. 1993). PTEs include interpersonal traumas such as rape, mugging, and physical assault as well as non-interpersonal traumas such as flood, fire, and motor vehicle accidents.

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PTEs also include witnessing death and injury to others and learning of the violent death or injury of a loved one. A meta-analysis examining gender differences in trauma exposure and posttraumatic stress disorder (PTSD) found that men are slightly more likely to report exposure to any PTE compared to women (Tolin and Foa 2006). However, exposure to specific types of PTSD varies greatly by gender.

Interpersonal PTEs

Interpersonal violence occurs over the life course, but it is especially common among children, adolescents, and young adults (e.g., Kilpatrick et al. 1992). For example, nearly 1 in 4 children in the United States has experienced physical, sexual, or emotional abuse (Finkelhor and Jones 2006), and comparable rates have been observed globally (Finkelhor 1994). Interpersonal trauma exposure also differs by gender such that girls and women are more likely to experience interpersonal violence such as sexual assault and childhood sexual abuse compared to boys and men (Kessler et al. 1995; Tolin and Foa 2006). For example, two meta-analyses of international studies of child sexual abuse (CSA) suggest that, on average, slightly less than 10 % of men reported CSA while 10–20 % of women reported CSA prior to age 18 (Finkelhor 1994; Pereda et al. 2009). In the United States, 1 in 5 women and 1 in 71 men have experienced a lifetime rape, defined as attempted or completed forced penetration or drug/alcohol facilitated penetration (Black et al. 2011). Approximately 1 in 3 US women and more than 1 in 4 US men (28.2 %) have experienced physical violence by an intimate partner (Black et al. 2011). These rates are consistent with those observed in other US samples (Walsh et al. 2015) and in other developed countries including Australia (Rees et al. 2011); however, the prevalence of violence exposure is considerably higher among women in developing and war-ravaged nations (Heise et al. 1994). For example, World Health Organization data from women aged 15–49 in multiple countries found that 15–71 % of ever-partnered women have experienced rape by an intimate partner and 5–65 % of women reported experiencing physical or sexual violence since age 15 by a non-partner (World Health Organization 2013). Pregnancy is also a period of potentially increased risk for violence exposure among women, with 3–32 % of women worldwide reporting abuse during the peripartum period (Campbell et al. 2004).

Non-interpersonal PTEs

In a nationally representative US survey, the most commonly reported PTEs included non-interpersonal violence such as the unexpected death of a loved one (25 %), serious illness, accident, or injury to a loved one (21 %), and indirect exposure to terrorism (e.g., watching the events of 9/11 unfold on television; 22 %) (Bohnert and Breslau 2011). In the same survey, 17–30 % of trauma-exposed persons reported experiencing a life-threatening accident and 16–25 % reported experiencing a natural disaster (Pietrzak et al. 2011). Numerous studies suggest that men are more likely than women to experience accidents, natural disasters or fires, witnessing death or injury, and combat or war (Kessler et al. 1995; Tolin and Foa 2006).

Outcomes

Posttraumatic Sequelae

Although stress disorder (PTSD) is the most commonly studied outcome of trauma exposure, most persons exposed to PTEs do not develop PTSD (Bonanno 2005). Indeed, despite the fact that nearly everyone will be exposed to at least one PTE during his or her lifetime (e.g., Bohnert and Breslau 2011), estimated lifetime rates of PTSD range from 4 to 14 % in the United States (Breslau 2002; Roberts et al. 2011). Globally, the prevalence of PTSD is relatively consistent, although higher prevalence of PTSD has been observed in countries with greater exposure to war and torture (Steel et al. 2009). Among US women and men, rape and combat exposure, respectively, are the PTEs associated with the highest conditional probability of developing PTSD (Kessler et al. 1995). Despite the fact that men are more likely to experience any PTE, women are more likely to develop PTSD once exposed to a PTE (Breslau 2002; Breslau and Anthony 2007; Tolin and Foa 2006). Indeed, women are twice as likely to develop PTSD when compared to men (Kessler et al. 1995), a finding that may relate to women's increased risk for sexual violence compared to men (Cortina and Kubiak 2006). Among women only, exposure to assaultive violence has been shown to both increase risk for PTSD both immediately as well as when exposed to later non-assaultive violence (Breslau and Anthony 2007).

Comorbidity

Among those persons who meet diagnostic criteria for lifetime PTSD following a PTE, the vast majority have significantly elevated risks for other lifetime disorders (Kessler et al. 1995; for review see Breslau 2002; Koenen et al. 2008a). Trauma-exposed persons with PTSD consistently have been found to have higher risk for suicide as well as anxiety, mood, and substance use disorders compared to those without PTSD (Breslau et al. 1997; Breslau 2002; Blanco et al. 2013; Kessler 2000). Other psychopathologies have been associated with trauma exposure and/or the development of PTSD including major depression (Cuijpers and Smit 2002; Cuijpers et al. 2013), suicidality (van Spijker et al. 2011), personality disorders (Walsh et al. under review), and substance use disorders (Rehm et al. 2009). In one study, the risk of suicidal ideation was five times higher for those with PTSD compared to those without (Kessler 2000). While PTSD and disorders like depression may share similar symptoms, PTSD may be a causal factor for other psychiatric and physical disorders, contribute to the severity of the comorbid conditions, or share common antecedents or vulnerabilities with the comorbidities (Breslau 2009; Koenen et al. 2008a; McLeod et al. 2001). Physical conditions associated with PTSD include increased chronic physical pain and somatization, cardiovascular conditions, autoimmune disorders, impaired immunity, and obesity (for review, see Qureshi 2009).

Significant gender differences also exist in patterns of comorbidity. For example, women with PTSD are more likely than men with PTSD to meet criteria for another anxiety disorder like Panic Disorder (e.g., 12.6 % versus 7.3 %; Kessler et al. 1995), while men with PTSD are more likely than women with PTSD to meet criteria for a substance use disorder (51.9 % vs. 27.9 % for AUD; 34.5 % vs. 26.9 % for drug use disorder) and

conduct disorder (43.3 % vs. 15.4 %) (Kessler et al. 1995). In a study of women only, the PTSD comorbidity with the highest lifetime prevalence was major depression, although women who developed PTSD were at increased risk for both major depression and AUD (Breslau et al. 1997).

Disability and Impairment

Beyond the development of psychiatric conditions, trauma exposure and PTSD also have been associated with significant functional impairment related to physical and psychiatric comorbidities as well as the chronicity of PTSD symptoms. Adverse consequences throughout the life course include increased risk for poor school performance, work impairment such as absenteeism (estimated at over 3.5 days of work missed per month due to PTSD), and unemployment (Kessler 2000). Other psychosocial impacts include marital instability and parenting challenges (Rodriguez et al. 2012; Kessler 2000). Given that PTSD has been found to persist beyond 2 years in about one-third of cases, the disease burden should not be neglected (Breslau 2009; Kessler et al. 1995). Female gender is a risk factor for chronicity of PTSD (Breslau and Davis 1992). Further, in estimating disease burden, resilience theories may be useful for public health planning and treatment. Studies of symptom trajectories following trauma exposure indicate that persons may experience varying levels of symptom severity over time in patterns that indicate, for example, recovery, chronic dysfunction, or relapsing/remitting (Norris et al. 2009). While a single disorder is associated with substantial functional impairment, comorbidity is associated with even greater costs to the individual and society. Thus, understanding how trauma exposure may give rise to or complicate this host of negative outcomes can improve existing prevention and intervention programs and potentially ameliorate the heavy social and economic burden of trauma exposure and related sequelae.

Psychobiology

A number of psychobiological factors may be important to consider the relationship between trauma exposure and posttraumatic sequelae including genetics, neural circuitry, and psychological phenomena.

Genetics

Genetic factors influence who is trauma exposed (e.g., Sartor et al. 2012) and who develops posttraumatic sequelae (e.g., Sartor et al. 2011). For example, twin studies suggest that 47–60 % of the variance in trauma exposure can be attributed to additive genetic factors (Lyons et al. 1993; Sartor et al. 2012), while 30–70 % of the variance in PTSD can be accounted for by genetic factors (Bailey et al. 2010; Sartor et al. 2011; Stein et al. 2002a; True et al. 1993). Heritability estimates for MDD range from 27 to 40 % (Kendler et al. 2006; Lyons et al. 1998; True et al. 1993; Sartor et al. 2012) while heritability estimates for alcohol dependence range from

55 to 71 % (Young-Wolff et al. 2012; Sartor et al. 2011; Ystrom et al. 2011). The genetic correlation between PTSD and MDD ranges from .77 (Koenen et al. 2008a) to 1.0 in one recent sample (Sartor et al. 2012) while the genetic correlation between PTSD and alcohol dependence has been estimated to be as high as .54 (Sartor et al. 2011). Overall, findings suggest that genetic heritability plays an important role in a range of common outcomes associated with PTE exposure, and some of the heritable influences on trauma exposure and related disorders may be shared.

Gene by environment (G×E) studies provide important information about the specific genetic variants that are associated with PTSD, MDD, suicidality, and substance use disorders. G x E studies are particularly well-suited to address genetic questions about PTSD as it is a phenotype that requires exposure to an environmental stressor (Koenen et al. 2009; Koenen et al. 2008b). Recent reviews of the G×E literature relating to PTSD have highlighted interactions between trauma exposure, particularly childhood abuse, and genes involved in the dopaminergic, serotonergic, and neuroendocrine systems (Cornelis et al. 2010; Nugent et al. 2008; Skelton et al. 2012) including the dopamine receptor (D2) and the dopamine transporter (DAT) (e.g., Drury et al. 2009; Segman et al. 2002), the *5-HTTLPR* polymorphism in the promoter region of the serotonin transporter gene (*SLC6A4*) (e.g., Wang et al. 2011; Xie et al. 2009), and *FKBP5*, a regulator of glucocorticoid receptor sensitivity that is involved in HPA axis stress reactivity (Binder et al. 2008; Mehta et al. 2012; Sarapas et al. 2011; for review see Yehuda et al. 2011; Xie et al. 2010). Many of the same genes have been shown to interact with trauma exposure to predict MDD, suicidality, and substance use disorders. For example, polymorphisms in *5-HTTLPR* (Grabe et al. 2012), brain-derived neurotrophic factor (BDNF; Tsai et al. 2003), and proinflammatory cytokine interleukin-18 (IL-18; Haastrup et al. 2012) have been linked to the development of MDD. Similarly, *D2, DAT*, and *5-HTTLPR* have been associated with alcohol dependence (for review see Dick et al. 2003), and 5-HTTLPR has been associated with risk for suicide (Roy et al. 2010). In addition to these associations, sex-specific differences have been noted in a G x E association between *GABRA2* genotype and environmental stressors on alcohol dependence such that men with the risk genotype who had more positive life events were less susceptible to alcohol dependence (Perry et al. 2013).

In addition to family/twin and candidate gene studies, other genetic methods are increasingly being used to study associations between genetics and the development of psychopathology among trauma victims. Genome-wide association studies (GWAS) have been employed to compare DNA markers on the genome in diseased persons as compared to persons free of symptoms of that disorder. Positive results have included an association between PTSD and the retinoid-related orphan receptor alpha (RORA) gene (Logue et al. 2013) and the Tolloid-Like 1 gene (*TLL1*; Xie et al. 2013). Furthermore, in women, a novel positive association has been observed between PTSD and the RNA gene, lincRNA *AC068718.1* (Guffanti et al. 2013) as well as the pituitary adenylate cyclase-activating polypeptide (PACAP) and PAC1 receptor, which broadly regulate the cellular stress response (Ressler et al. 2011). Although some studies have failed to support the PACAP finding (Chang et al. 2011), other replications have garnered support for this association (Uddin et al. 2013). With

regard to substance use disorders, GWAS studies have confirmed associations between alcohol dependence and *ADH1B* and *ADH1C*, while identifying novel risk loci on chromosomes 4 and 2 and population-specific markers on chromosomes 5, 9, and 19 (Gelernter et al. 2014).

Epigenetic mechanisms, which are heritable changes in gene expression or functionality that do not involve changes to the underlying DNA sequence, also may partially explain the development of negative sequelae among trauma-exposed persons. DNA methylation, which involves the addition of a methyl group to the 5 position of the cytosine pyrimidine ring or the number 6 nitrogen of the adenine purine ring, has been the most widely studied with regard to trauma exposure and posttraumatic sequelae. For example, animals exposed to a psychosocial stressor evidence increased DNA methylation in the hippocampus (Chertkow-Deutsher et al. 2010; Roth et al. 2011; Zhang et al. 2010), and there is evidence that these epigenetic modifications can be passed to offspring (e.g., Franklin et al. 2010). Human studies suggest that childhood trauma exposure is associated with methylation in specific genes, including the promoter region of the serotonin transporter (Beach et al. 2010, 2011; Smith et al. 2011) and the glucocorticoid receptor (McGowan et al. 2009). Microarray methylation studies have identified differences in methylation patterns for persons with and without PTSD and MDD (Fuchikami et al. 2011; Smith et al. 2011; Uddin et al. 2010, 2011). Finally, studies that integrate gene expression and methylation data have found evidence of different psychobiological pathways for PTSD among those with and without histories of childhood trauma (Mehta et al. 2013). A recent review of sex differences in DNA methylation associated with PTSD and depression suggests that neurodevelopmental changes in methylation may lay the groundwork for stress differences in reactions to stress that give rise to gender differences in the prevalence of stress-related disorders (Uddin et al. 2013). Specifically, in rodent models, sex-specific methylation at CpG sites in the estrogen receptor interacts with neonatal hormone exposure during sensitive periods to differentially effect brain development that could, in part, explain females' increased susceptibility to psychopathology in adulthood (Kurian et al. 2010; Schwarz et al. 2010).

Neural Circuitry

Trauma exposure also may influence the development of negative sequelae through structural or functional changes in the brain. A meta-analysis of brain imaging studies suggests that trauma exposure is associated with reduced volume in the hippocampus, a brain region implicated in episodic memory, relative to non-trauma exposed controls, and trauma victims with PTSD evidence even greater reductions in hippocampal volume compared to trauma victims without PTSD (Woon et al. 2010). Most brain imaging studies are cross-sectional, which limits conclusions about whether trauma exposure and PTSD decrease hippocampal volume or predispose persons to develop PTSD when exposed to a PTE. However, at least one study using monozygotic twins discordant for trauma exposure indicated that reduced

hippocampal volume is a preexisting risk factor for PTSD when exposed to PTEs, not an outcome of exposure to trauma (Gilbertson et al. 2002). Persons with PTSD and depression also show similar reductions in prefrontal cortex volume when compared to trauma-exposed healthy controls (Kroes et al. 2011). There is evidence of gender differences in brain development among children with and without child maltreatment histories and PTSD such that maltreated boys with PTSD evidence diminished volume in the corpus callosum and cerebrum and increased lateral ventricular volume relative to maltreated girls with PTSD and health controls (De Bellis and Keshavan 2003).

Neuroendocrine Pathways

Alterations in the hypothalamic-pituitary-adrenal (HPA) axis, the primary system involved in the physiological stress response (Sapolsky et al. 2000), have been observed among child abuse victims (e.g., Cicchetti et al. 2010; Shea et al. 2005; Trickett et al. 2010), sexual assault victims (e.g., Resnick et al. 1995; Yehuda and Bierer 2009), combat veterans (e.g., Boscarino, 1996), and motor vehicle accident survivors (Delahanty et al. 2000). In general, trauma victims evidence hypocortisolism, although one study found heightened daily cortisol among women with sexual abuse histories (Lemieux and Coe 1995). Blunted HPA axis responsivity also has been associated with the development and chronicity of PTSD among trauma victims (e.g., Bremner et al. 2003; Walsh et al. 2014; Yehuda et al. 1990). However, heightened cortisol responsivity has been observed among trauma victims with depression when exposed to psychosocial stressors (Burke et al. 2005). Thus, despite clear indications that trauma exposure is associated with HPA axis dysregulation, associations between common trauma-related sequelae like PTSD and depression and HPA axis functioning remain less clear. One study has suggested that prolonged childhood abuse, rather than the development of PTSD, MDD, or even BPD symptoms was associated with hyperresponsivity in the HPA axis (Rinne et al. 2002).

Psychological Factors

Trauma exposure may also influence the development of negative outcomes through cognitive and/or behavioral processes including shame, self-blame, cognitive distortions, and dysregulation in emotion regulation or coping. Developed to explain the negative sequelae of childhood sexual abuse, Finkelhor and Browne's (1985) traumagenic dynamics theory suggests that early life abuse can negatively shape a child's perception of his/herself, his/her behavior, and his/her interpersonal relationships, through four psychological processes that include traumatic sexualization, betrayal, shame/guilt, and powerlessness. These dynamics in turn have been associated with increased distress including PTSD, depression, and substance use disorders among victims of violence (Canton-Cortes et al. 2012; Walsh et al. 2014). Cognitive distortions including self-blame, hopelessness, and

preoccupation with danger also have been associated with more severe PTSD and with brain activation in regions that have previously been implicated in visual processing and autobiographic memory recall (Daniels et al. 2011). Cognitive distortions are also common among women dually diagnosed with PTSD and substance use disorders (Najavits et al. 2004).

Emotional dysregulation, which reflects difficulties identifying, modulating, and expressing emotions (Gratz and Roemer 2004; Gross 1998), is another domain of functioning that may be disrupted among victims of sexual violence. For example, families in which violence is occurring may provide few opportunities for children to observe and model emotion regulation abilities that allow for effective modulation of chronic negative affect. To cope, they may become emotionally or experientially avoidant, and when avoidance does not ameliorate distress, they may develop psychopathology (e.g., PTSD, MDD) and engage in external coping mechanisms including substance abuse and risky sexual behavior (Polusny and Follette 1995).

Support for emotion regulation and maladaptive coping or self-medication as explanatory mechanisms in the link between trauma exposure and negative sequelae stems from research documenting that emotion dysregulation underlies PTSD and MDD (e.g., Tull et al. 2007), and those with trauma histories report greater use of substances to reduce both negative affect (Grayson and Nolen-Hoeksema 2005) and PTSD symptoms (Miranda et al. 2002; Ullman et al. 2005). Hyperarousal symptoms, in particular, are associated with increased alcohol and drug use and dependence (e.g., Reed et al. 2007), and victims who report drinking to cope with distress or to reduce tension are more likely to develop problem drinking behaviors including alcohol abuse/dependence, blackouts, and increased tolerance (Ullman et al. 2005).

Diagnosis

Posttraumatic Stress Disorder

The most commonly assessed and diagnosed condition among trauma victims is posttraumatic stress disorder (PTSD). PTSD as defined in DSM-5 requires: (A) exposure to a PTE; (B) at least one of five possible reexperiencing symptoms (e.g., distressing thoughts/dreams, intense physiological/psychological responses to reminders of the trauma); (C) one of two possible avoidance symptoms (e.g., avoiding internal thoughts or feelings or external reminders of the trauma); (D) two of seven cognitive or mood-related symptoms (dissociative amnesia, persistent self-blame, persistent negative beliefs or emotions, constricted affect, anhedonia, or feelings of alienation); and (E) two of six arousal symptoms (e.g., sleep problems, irritability, heightened startle response, self-destructive behaviors, irritability/aggressiveness). Symptoms must be experienced with at least moderate frequency and severity in the previous month, and they must be associated with some degree of social or occupational functional impairment to yield a diagnosis.

Developmental Considerations

The DSM-5 also includes a developmental subtype of PTSD for children younger than 6 years old. Children younger than age 6 may lack the vocabulary and meta-awareness to describe their symptoms; therefore, DSM-5 criteria for preschool PTSD are more behaviorally grounded. With regard to reexperiencing symptoms, children do not always display overt distress when recollecting PTEs; therefore, no affect or excitement that accompanies a PTE recollection could qualify as a reexperiencing symptom. Only one symptom in the avoidance or negative alterations in cognitions and mood is necessary as these are the least frequent PTSD symptoms (Scheeringa et al. 2006). The wording of the symptoms "diminished interest in significant activities" and "feelings of detachment or estrangement" were changed to "constricted play" and "social withdrawal" for children under age 6. The arousal symptoms are already conducive to behavioral assessment; therefore, only the irritability symptom was changed to "extreme temper tantrums."

Depression

Frequently comorbid with PTSD (Nixon et al. 2004; Stein and Kennedy 2001), a diagnosis of depression requires depressed mood or anhedonia most days for the previous 2 weeks. It can also include significant changes in weight, appetite, or sleep, fatigue, guilt or feelings of worthlessness, problems with concentration, and suicidal ideation.

Other Anxiety Disorders

Approximately 70 % of trauma-exposed treatment-seeking patients report panic attack symptoms (Falsetti and Resnick 1997). Panic attack symptoms include heart palpitations, sweating, trembling/shaking, shortness of breath, a choking feeling, chest pain, nausea, feeling dizzy/lightheaded, derealization/depersonalization feelings, fear of losing control/going crazy, fear of dying, numbness/tingling, and chills/hot flashes. A panic attack is defined as experiencing four or more of these symptoms without warning or provocation; panic disorder refers to recurrent, unexpected panic attacks. Panic disorder cannot be diagnosed if the attacks only occur when exposed to a traumatic reminder.

Substance Use and Disorders

Trauma exposure has been associated with elevated risk for substance use disorders (Fetzner et al. 2011; Mills et al. 2006; Rees et al. 2011; Walsh et al. 2014); however, some research suggests that it is the development of PTSD, and not trauma exposure itself, that accounts for heighted risk for substance use and disorders (for review see

Breslau 2002). According to the self-medication model of substance use, trauma-exposed persons who develop PTSD, other anxiety symptoms, or depression may use substances to cope with these distressing symptoms (Khantzian 1997).

Evaluation

Clinical Interviews

Psychiatric conditions associated with PTE exposure have been assessed using various tools. The gold standard clinical interview for diagnosing PTSD is the Clinician Administered PTSD Scale (CAPS), which takes approximately 1 h to administer and includes a thorough evaluation of lifetime PTE exposure and the 17 PTSD items identified in the DSM-IV. Respondents are asked to separately rate the frequency and severity of each symptom in the preceding 2 weeks. The CAPS has been shown to have excellent reliability and validity, and consistent scores have been observed across items, raters, and testing occasions (Weathers et al. 2001). With regard to substance use, the Timeline Follow-back interview (Sobell and Sobell 1996) is a validated method to gather data on the patterns and frequency of substance use using a calendar method. The Structured Clinical Interview for DSM-IV also has been used extensively to diagnose PTSD, depression, other anxiety disorders, substance use disorders, and personality disorders.

Self-Report Measures

Although no substitute for diagnostic clinical interviews, a number of self-report measures with excellent reliability have been developed and validated against the gold standard clinical interviews. The PTSD Checklist (PCL; Weathers et al. 1999) has been developed in three formats – Civilian, Military, and Specific. Each version contains the 17 PTSD items from the DSM-IV and requires participants to rate their symptoms on a 0–4 severity scale. The Modified PTSD Symptom Scale-Self-Report (PSS-SR; Foa et al. 1993) is another 17-item measure of PTSD as assessed in the DSM-IV. Each symptom criterion is rated in terms of frequency of symptoms within the past 2 weeks on a scale of 0 = *not at all or only one time* to 3 = *almost always or five or more times per week*. Total scores range from 0 to 51. The PSS-SR has been shown to correlate highly with interview-based measures of PTSD (Foa et al. 1993) and has been used in numerous longitudinal studies assessing PTSD symptoms over time (e.g., Dunmore et al. 2001; Mayou et al. 2002). Measures such as the Davidson Trauma Scale, a self-report that separately assesses the frequency and severity of each DSM-IV symptom in the previous week on a scale from 0 to 4, also have been used to assess PTSD symptoms, particularly in SSRI trials (Davidson et al. 1997; 2002). Normative scores have been computed for comparison to the general population (Davidson et al. 2002).

Validated self-report measures for depression include the 21-item Beck Depression Inventory (BDI; Beck et al. 1988) and BDI-II (Dozois et al. 1998; Steer et al. 1997). The World Health Organization also has developed the Composite International Diagnostic Interview (CIDI; Wittchen 1994) that has been used in a number of epidemiologic studies (Kessler and Üstün 2004). Validated self-report measures for substance use and disorders include the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al. 1993), a 10-item self-report measure of alcohol use and related problems, and the Drug Abuse Screening Test (DAST-10, Skinner 1982), a 10-item self-report measure of drug use and related problems.

Assessments for Children

The Child Behavior Checklist (CBCL; Achenbach et al. 2002) is a parent/teacher rated scale that measures broad aspects of internalizing and externalizing pathology including anxiety, depression, and anger; however, the CBCL does not capture aspects of functioning that may be particularly related to trauma exposure including intrusions, avoidance, and arousal. The Trauma symptom Checklist for Young Children is a 90-item caretaker completed checklist that assesses eight clinical scales including PTSD Intrusions (PTS-I), Avoidance (PTS-AV), Arousal (PTS-AR), and Total symptoms (PTS-TOT) as well as Sexual Concerns (SC), Dissociation (DIS), Anxiety (ANX), Depression (DEP), and Anger/Aggression (ANG) (Briere et al. 2001). The UCLA PTSD Index (Decker and Pynoos 2004) contains a thorough assessment of trauma exposure as well as the 17 items of PTSD in the DSM-IV. The Children's Depression Inventory (CDI) is a 27-item self-report scale appropriate for children age 7 to 17 that has good reliability and validity with normative scores to facilitate age comparisons (Kovacs 2004).

Pharmacotherapy

Numerous medications have been shown to effectively treat PTSD including tricyclic antidepressants, monoamine oxidase inhibitors, and serotonin reuptake inhibitors (SSRIs); however, SSRIs show the greatest efficacy with the fewest side effects (Albucher and Liberzon 2002). SSRIs such as sertraline, paroxetine, and fluoxetine are commonly prescribed to treat the symptoms of PTSD (Asnis et al. 2004), with sertraline and paroxetine producing reductions in PTSD symptoms in randomized controlled trials (Brady et al. 2000), and receiving FDA approval for the treatment of PTSD in adults. Some sex differences have been found with regard to treatment response to SSRIs. Specifically, women show a more positive treatment response to SSRIs compared to men (Khan et al. 2005; Young et al. 2009). For example, in depressed outpatients, women had a more positive response to the SSRI sertraline compared to the tricyclic imipramine, and men showed a stronger response to imipramine compared to sertraline (Kornstein et al. 2000). Sex hormones appeared to

play a role in treatment response as premenopausal women responded better to sertraline compared to imipramine, while postmenopausal women responded equally well to both medications (Kornstein et al. 2000). To date, no medications have been approved for use in children (Drury and Henry 2012). In PTSD patients with limited responsivity to SSRI treatment, augmentation with an atypical antipsychotic, Olanzipine, has been shown to produce better outcomes (Stein et al. 2002b). While psychopharmacologic interventions can be part of effective treatment for PTSD, findings are limited by high dropout rates in clinical trials, and negative side effects of these medications may explain poor retention in clinical trials (Albucher and Liberzon 2002).

Psychotherapy

A number of exposure-based treatments have been shown to be effective for the treatment of PTSD. For example, Prolonged Exposure (PE), which requires participants to use imaginal exercises to expose themselves to the memory of their PTE and the physical sensations and thoughts that arose during the PTE (Foa et al. 2007), has evidenced large effect sizes for the treatment of PTSD (Powers et al. 2010). PE was originally designed to treat PTSD associated with sexual violence (Foa et al. 1991), but has successfully been extended to other populations including combat veterans and adolescents (Gilboa-Schechtman et al. 2010).

Cognitive Processing Therapy (CPT), which exposes patients to the thoughts and emotions associated with their PTE through a combination of writing and thought challenging exercises, also has been shown to be effective in reducing PTSD symptoms (Resick et al. 2002). However, CPT contains modules that specifically address guilt, shame, and interpersonal difficulties, and thus yields greater reductions in guilt when compared to PE (Resick et al. 2002). Furthermore, dismantling studies have shown that the cognitive component alone has a stronger effect on reducing symptoms compared to the writing component alone (Resick et al. 2008).

Eye Movement Desensitization and Reprocessing (EMDR), which involves imaginal exposure while receiving bilateral sensory input that encourages eye movements, is another form of exposure treatment that shows similar reductions to those found with PE and greater reductions in symptoms relative to a wait-list control (Rothbaum et al. 2005). Meta-analyses support these findings by showing that EMDR is equally efficacious relative to trauma-focused cognitive behavioral therapy such as PE and CPT (Seidler and Wagner 2006).

Stress Inoculation Training (SIT), which involves psychoeducation and coping skills to increase resilience to stress (Meichenbaum 1974), has been applied to trauma victims (Veronen and Kilpatrick 1989). At posttreatment, SIT has been shown to be more effective at reducing PTSD symptoms than supportive counseling or a wait-list control (Foa et al. 1991); SIT and PE were associated with comparable posttreatment reductions in PTSD, although PE was associated with further reductions in PTSD at 3 months follow-up (Foa et al. 1991). In a follow-up study, PE was associated with greater posttreatment reductions in anxiety, social adjustment, and

PTSD severity when compared to SIT, SIT plus PE (SITP), or a wait-list control (Foa et al. 1999). In a separate investigation comparing EMDR to SITPE, EMDR was associated with greater reductions in reexperiencing symptoms relative to SITPE (Lee et al. 2002).

Psychotherapies for Children

Trauma-focused cognitive behavioral therapy is a developmentally appropriate evidence-based treatment for trauma symptoms among trauma-exposed children (Cohen et al. 2004; Deblinger et al. 2006, 2011). TF-CBT involves the child and non-offending caregiver and includes psychoeducation, coping skills, and in vivo exposure through the construction of a trauma narrative that can be completed in a developmentally appropriate manner. TF-CBT has been shown to improve trauma symptoms, parenting skills, and child personal safety skills (Deblinger et al. 2011).

Treatments for Comorbid Conditions

As noted previously, PTSD and SUDs are frequently comorbid. However, conventional wisdom has often suggested that treating PTSD using difficult exposure techniques in a person with an active SUD may exacerbate the SUD. Consequently, many PTSD treatment programs require patients to receive SUD treatment prior to beginning PTSD treatment. However, patients are often disconnected from services when transitioning from one provider to another, suggesting that evidence-based treatments targeting multiple conditions are much needed. During the past decade, several studies have begun to highlight promising results for the simultaneous treatment of comorbid conditions. For instance, cognitive behavioral treatment for women with PTSD and SUD has been shown to reduce PTSD and SUD symptoms at 3 months follow-up compared to women in a wait-list control group (Cohen and Hien 2006). PE for women with comorbid PTSD and SUD has been shown to reduce PTSD symptoms without increasing SUD symptoms (Mills et al. 2012). CPT also is effective at reducing PTSD symptoms among veterans with comorbid PTSD and AUD (Kaysen et al. 2013). Women with comorbid PTSD and SUD who were randomized to trauma-focused therapy versus a health education program evidenced greater reductions in PTSD symptoms and those who maintained these reductions were more likely show substance use improvement (Hien et al. 2010). Imaginal and in vivo exposure therapy for PTSD plus cognitive behavioral treatment for cocaine dependence was associated with significant pre-post reductions PTSD symptoms and cocaine use (Brady et al. 2001); however, a high degree of dropout was noted. Finally, a recent study examining combined PE and naltrexone for the treatment of comorbid PTSD and AUD found that the combined approach was associated with greater reductions in drinking days relative to either of the individual approaches (Foa et al. 2013).

PTSD is also highly comorbid with mood and other anxiety disorders and symptoms including depression and panic attacks. Given its focus on changing cognitive distortions that may be shared by both PTSD and MDD, CPT has been shown to result in concurrent changes in PTSD and depression symptoms (Liverant et al. 2012). Multiple channel exposure therapy, an evidence-based treatment that includes exposure to panic symptoms as well as imaginal exposure to the PTE, has been shown to effectively reduce comorbid PTSD and panic attacks (Falsetti et al. 2005, 2008). Other comorbid problems like affect dysregulation or interpersonal difficulties that are frequently present among trauma-exposed persons with PTSD may be targeted through treatments like Skills Training in Affective and Interpersonal Regulation (STAIR) followed by exposure therapy. Adult women with child sexual abuse histories who participate in STAIR evidence reductions in PTSD symptoms as well as affect dysregulation and interpersonal problems compared to wait-list controls (Cloitre et al. 2002).

Conclusions

Trauma exposure is prevalent and associated with a wide range of mental health and substance use disorders. Although men are slightly more likely to be exposed to any PTE, women are twice as likely to develop PTSD when exposed. The etiology of gender differences in posttraumatic sequelae may have yet to be elucidated, but may include genetic, neural circuitry, and psychological phenomena. Valid and reliable interviews and self-report measures are available for the assessment of trauma-related conditions. Changes have been made to the criteria for PTSD in DSM-5. Comorbidity is the rule rather than the exception among trauma-exposed persons; however, only in the last decade have treatment outcome studies shown that multiple co-occurring outcomes can be targeted simultaneously. Whether there are gender differences in treatment, response or treatment matching deserves further examination. Despite a large body of work on gender, trauma exposure, and trauma-related disorders, more research is needed to identify the mechanisms by which gender shapes response to PTEs and treatment for posttraumatic sequelae.

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Anxiety and Related Disorders in Women

Katherine Sevar, Bavi Vythilingum, and David Castle

Anxiety does not empty tomorrow of its sorrows, but only empties today of its strength (Charles Spurgeon)

Anxiety disorders are highly prevalent and persist across the life course. As documented in earlier chapters of this volume, women are particularly prone to anxiety disorders, with around a third meeting diagnostic criteria over the course of a lifetime (Alexander et al. 2007). In this chapter, we will summarize some key points pertaining to the epidemiology, clinical presentation, and treatment of anxiety disorders in women. We will also address the comorbidity between physical illness and anxiety disorders in women. Finally, we will examine the specific challenges faced in treating women with anxiety disorders during pregnancy and lactation.

Epidemiology

Kessler et al. (2012) found the prevalence of anxiety disorders in women in the USA were as follows: specific phobia 12.1 %; social phobia 7.4 %; post-traumatic stress disorder 3.7 %; generalized anxiety disorder 2.0 %; separation anxiety disorder 1.2 %; panic disorder 2.4 %; agoraphobia 1.7 %; obsessive-compulsive disorder (OCD) 1.2 % (Kessler et al. 2012). In an Australian study, Williams et al. (2010) used the Structured Clinical Interview for DSM-IV TR Axis-I Disorders, non-patient edition (SCID-I/NP) to report the prevalence of anxiety and mood disorders, in an age-stratified representative sample of women aged 20 years and older (Williams et al. 2010). The median age of onset of anxiety disorders was 18.5 years and the prevalence of anxiety disorders in women across the life course was 13.5 % with panic disorder (5.5 %) and specific phobias (3.5 %) being the most common.

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The preponderance of these conditions in women is not well understood. In a prospective, longitudinal, population-based study of 643 women, psychosocial variables were examined to evaluate whether it was possible to predict the onset of a new anxiety disorder or the recurrence of an existing disorder. The presence of anxiety disorders was assessed every 6 months over a 3-year period, using the Structured Clinical Interview for the Diagnosis of Axis I Disorders (SCID-I). It was found that focusing on negative life events was not a predictor of the onset of anxiety either alone or in interaction with other variables. Significant predictors of anxiety included a history of anxiety, increased anxiety sensitivity (i.e., fear of anxiety-related sensations), and increased neuroticism (Calkins et al. 2009).

The complex interplay between genetic risk factors and environmental influences was studied by Hetteam and colleagues (2005) who reported that there were no differences between the sexes with regard to the vulnerability to develop anxiety disorders. However, these authors suggested that the development of anxiety disorders could be split across the both sexes: firstly, "panic-generalized-agoraphobic anxiety" and secondly, the "specific phobias." They suggested that the underlying etiology of both of these groups is best explained by the presence of two genetic factors which are additive and common across the disorders, with one genetic factor contributing a more causative role to the first subset of "panic-generalized-agoraphobic anxiety" and a second genetic factor contributing to the second subset of "specific phobias." Social anxiety disorder (SAD) was influenced by both genetic factors (Hettema et al. 2005).

Social Anxiety Disorder (SAD)

Social anxiety disorder (SAD) affects men and women almost equally with approximately 15 % of women and 11 % of men affected across the life course (Kessler et al. 2005). SAD usually begins in childhood or early adolescence and maintains a chronic course throughout adulthood. The clinical features include experiencing extreme anxiety in social scenarios due to a fear of embarrassment or ridicule. Sufferers often manifest physical signs such as blushing and stuttering if asked to speak in public. People with social phobia may become avoidant of social situations and there is some difference between sexes with women stating that they have more distress when speaking in public or meeting strangers (Turk et al. 1998).

Treatment

Psychological therapies for SAD focus on assertiveness training, cognitive behavioral therapy (CBT) and graded exposure to overcome avoidance behavior (Rodeburgh et al. 2004). Meta-analyses have suggested that individual and group CBT may work equally well for individuals with SAD (Rodebaugh et al. 2004; Liber et al. 2008), and that women and men respond equally well to CBT (Canton et al. 2012).

Panic Disorder

Estimates suggest 1–2 % of the adult population suffer panic disorder (Yates 2009). Common risk factors for the development of panic disorder include female gender, low socioeconomic status, and an anxious temperament in childhood. Panic disorder is associated with an elevated risk of suicide as well as all-cause mortality and cardiovascular disease. It ranks highest among the anxiety disorders in terms of disease burden. There has been interest in the conceptualization of anxiety disorders as resulting from psychopathology during childhood, in particular in relation to the presence of separation anxiety disorder in childhood. A meta-analysis of 20 studies indicated that children with separation anxiety disorder were more likely to develop panic disorder in adulthood (odds ratio (OR) = 3.45; 95 % confidence interval [CI] = 2.37–5.03). Additionally, five studies suggested that a childhood diagnosis of separation anxiety disorder increased the overall risk of the development of future anxiety disorders in adulthood (OR = 2.19; 95 % CI = 1.40–3.42) (Kossowsky et al. 2013).

Recent research has focussed on the gene encoding monoamine oxidase A (MAOA) in women. This has been of particular interest given the effectiveness of MAO inhibitors in the treatment of panic disorder and previous studies of MAO inhibitors in animal models of panic disorder. A meta-analysis of four studies reported a significant female-specific association when calculating an allelic model in panic disorder, leading the authors to suggest that "this sex-specific effect might be explained by a gene-dose effect causing higher MAOA expression in females." Furthermore, they hypothesized that high-expression MAOA-uVNTR alleles significantly increase the risk of developing panic disorder in women. This finding will require further replication in larger samples, but may be a lead in the understanding of female vulnerability to the development of panic disorder (Reif et al. 2012).

Panic disorder has been reported as having a prevalence of between 1.3 and 2.0 % in pregnancy (Sholomskas et al. 1993). While in the postpartum period both an increased risk of relapse as well as increased risk of new onset panic disorder has been reported, the risk in pregnancy per se is not known (Sholomskas et al. 1993). There are conflicting data about the course of panic disorder in pregnancy. Some studies report improvement of symptoms (Wisner et al. 1996; Cohen et al. 1994); such improvements have been linked to physiologic changes in hormonal milieu and progesterone metabolites, as well as attenuation of the noradrenergic response to stress (Majewska et al. 1986; Barron et al. 1986). Other studies have reported either no change or worsening of symptoms. It may be that the best predictor of symptom change is pregravid symptom severity, with greater severity predicting a worse course (Ross and McLean 2006). Chen et al. (2001) found that in women with panic disorder who actually experienced panic attacks during pregnancy, there was an increased risk of having small-for-gestational-age infants and the adjusted odds ratio for having a preterm delivery was 2.54 (95 % CI = 1.09–5.93).

Treatment

Cognitive behavioral therapy (CBT) is again the first-line psychotherapy treatment for panic disorder. Pharmacotherapy, particularly selective serotonin reuptake inhibitors (SSRIs) are also a first-line option (Mitte et al. 2005). A recent review (Stein et al. 2010) also suggested efficacy when combining SSRIs with CBT. (See chapter "Anxiety and related disorders in men" for greater detail).

Generalized Anxiety Disorder

Women with generalized anxiety disorder (GAD) report intrusive, pervasive worries that affect their function and quality of life across many domains (Grant et al. 2005). GAD usually has an onset prior to 25 years old and most often has a chronic course throughout adulthood (Stein et al. 2005). In the USA, generalized anxiety disorder was second only to substance abuse in terms of population prevalence (Fricchione 2004). Individuals with generalized anxiety disorder have a significantly increased risk of developing subsequent depression (Hettema et al. 2006) with up to 75 % developing a major depressive episode in their lifetime. The risk factors for the development of generalized anxiety disorder include a family history of the disorder or stress and trauma. Individuals with comorbid generalized anxiety disorder and depression are more disabled than those with either disorder alone (Grant et al. 2005).

A neurobiological model of generalized anxiety disorder suggests that the early life experience of an increased circulation of adrenaline and cortisol, as a result of exposure to stressful situations, may lead to increased upregulation, and hypersensitivity, of the HPA axis in adulthood. The role of the transgenerational transmission of generalized anxiety disorder is worth considering in this context given that the infants of women with anxiety disorders in pregnancy are more likely to be exposed to greater circulating levels of adrenaline in utero, meaning that they are more vulnerable to developing anxiety disorders in childhood if exposed to early life trauma.

There is little data on the epidemiology of GAD in pregnancy. One study found a rate of 8.5 % in the third trimester (Shear and Oommen 1995). There are few data on the course of pre-existing GAD in pregnancy. Diagnosing GAD poses special challenges in pregnancy – it is normal to have degree of worry and anxiety in pregnancy.DiPietro et al. (2002) developed the Pregnancy Experiences Scale which in addition to measuring worry also measures uplifts (the positive emotional experiences of pregnancy) (DiPietro et al. 2002). In a sample of well pregnant women the majority endorsed both worries and uplifts, and thoughts about normality of baby endorsed by over 80 % of the sample (DiPietro et al. 2002).

Treatment

The psychotherapy treatment of choice for generalized anxiety disorder is cognitive behavioral therapy with women and men both responding in equal measure (Yonkers et al. 2003). There has been some recent evidence suggesting that applied relaxation

techniques could be as useful as cognitive behavioral therapy (Cujipers 2014). Pharmacotherapy in generalized anxiety disorder has an effect size of 0.6 (Gould et al. 1997), and SSRIs would be considered the first-line treatment.

Specific Phobias

Specific phobias are lasting or unreasonable fears of specific objects or situations which often pose little or no real danger. If an individual is exposed to this situation, they experience severe anxiety symptoms and therefore seek to avoid situations of exposure which may lead to significant functional impairment and limitations.

Specific phobias are usually characterized by early age of onset and high rates of comorbidity. A 17-month prospective study from Germany found that women with a specific phobia were twice as likely to develop another anxiety disorder, in particular, generalized anxiety disorder and somatoform disorder when followed over a 17-month period (Trumpf et al. 2010). The same group of researchers also investigated the predictors of specific phobias in women and found that high levels of pre-existing psychopathology, a lack of coping skills, and a negative cognitive style were all associated with increased incidence of specific phobias. They suggest that identifying these risk factors may aid in identifying individuals who are at increased risk of the development of specific phobias and may lead to an improvement in the prevention of these conditions (Trumpf et al. 2010).

Treatment

Psychological therapy, namely, exposure therapy as part of CBT, is the first-line treatment for specific phobias although only a small minority of individuals seek treatment, as low as 8 % (Stinson et al. 2007). A meta-analysis conducted in 2008 (Wolitzky-Taylor et al. 2008) found that exposure-based psychological treatments were effective in the treatment of specific phobias.

Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD) is estimated to have been the fifth leading cause of disability for women aged 15–44 years in developed countries (Murray and Lopez 1996), and epidemiological surveys suggest that the condition afflicts women more frequently than men (Bebbington 1990) although clinical studies show a less marked female excess, which may reflect differences in help-seeking behavior and a more severe illness course in men (Castle et al. 1995; Lensi et al. 1996; Noshirvani et al. 1991). Additionally, men tend to have an earlier onset of OCD than their female counterparts (Castle et al. 1995; Lensi et al. 1996; Lochner et al. 2004).

There are also sex differences between the type of symptoms manifested in OCD with women more likely to manifest contamination fears and cleaning rituals and

men more prone to aggressive and sexual obsessions, and symmetry concerns (Lensi et al. 1996; Bogetto et al. 1999).

Women with obsessive-compulsive disorder (OCD) sometimes report that symptoms first appear or exacerbate during reproductive cycle events and there has been recent research which has demonstrated the relationship between OCD and the reproductive cycle in women. A meta-analysis revealed that the prevalence of OCD increased during pregnancy (mean = 2.07 %) and even more so in the postpartum period (mean = 2.43 %) compared with the general population (mean = 1.08 %). Additionally, both pregnant (mean = 1.45) and postpartum (mean = 2.38) women were at greater risk of experiencing OCD compared to the general female population, with an aggregate risk ratio of 1.79 (Russell et al. 2013).

Further research has focussed on OCD across the reproductive cycle including at menarche, premenstruum, pregnancy, postpartum, and at menopause. In a survey of 542 women (United States, $n = 352$; Dutch, $n = 190$) using a self-report questionnaire of symptoms across time, a significant relationship between exacerbations of OCD and various phases of the reproductive cycle was found. OCD onset occurred within 12 months after menarche in 13.0 % of participants; during pregnancy in 5.1 %; postpartum in 4.7 %; and at menopause in 3.7 %. It was evident that worsening of pre-existing OCD occurred at reproductive cycle events with 37.6 % of women reporting worsening of symptoms at premenstruum, 33.0 % during pregnancy, 46.6 % in postpartum period, and 32.7 % at menopause. Furthermore, a first pregnancy was significantly associated with exacerbation in second pregnancy (OR = 10.82, 95 % CI = 4.48–26.16); similarly, postpartum exacerbation in a first pregnancy was associated with an elevated risk in ensuing pregnancies (OR = 6.86, 95 % CI = 3.27–14.36). These findings reinforce the importance of clinical vigilance during these phases of the reproductive cycle (Guglielmi et al. 2014).

Treatment

The main psychological therapy in the treatment of OCD is exposure and response prevention (ERP) (Abramowitz 1997) and this is often used in combination with SSRI medications.

Physical Illness and Anxiety Disorders in Women

There is an increased prevalence of anxiety disorders in the presence of chronic physical illness when compared to the prevalence of anxiety disorders in individuals without chronic physical illness. These disorders include chronic fatigue syndrome, fibromyalgia, gastrointestinal conditions, and bronchitis. Anxiety disorders which are comorbid with physical illness have also been significantly associated with short-term disability, requiring help with instrumental daily activities, and suicidal ideation (Gadalla 2008). These findings highlight the importance of screening for the presence of anxiety disorders in women with chronic physical illnesses given

the potential for detrimental impact on their quality of life and level of disability associated with their chronic physical illness.

The relationship between anxiety disorders and physical illness appears bidirectional as the incidence of certain medical conditions appears to be higher in patients with anxiety disorders. A study conducted over 10 years in Canada (Bowen et al. 2000) showed that individuals with anxiety disorders, in comparison to those without, had a significantly higher relative risk of developing medical diseases. The highest hazard ratio was for cerebrovascular disease (hazard ratio = 2.0, 95 % CI = 1.09–3.65); hazard ratios were also significant for ischemic heart, gastrointestinal, respiratory diseases as well as hypertension (Bowen et al. 2000).

Heart Disease

Anxiety has been associated with the development and recurrence of coronary heart disease. Tordaro et al. (2007) reviewed the prevalence of anxiety disorders in men and women with established coronary heart disease and reported that 36.0 % ($n=54$) met the diagnostic criteria for a current anxiety disorder, while 45.3 % ($n=68$) had a past history of an anxiety disorder. Female cardiac patients had significantly higher current (women = 58.3 % vs. men = 25.5 %, $p<0.001$) and lifetime (women = 70.8 % vs. men = 33.3 %, $p<0.001$) rates of anxiety disorders compared with male participants (Todaro et al. 2007). Special efforts are needed to screen patients for anxiety disorders when attending outpatient cardiology or cardiac rehabilitation.

Cancer

There has been a considerable amount of research into the prevalence of anxiety disorders in women with cancer. A meta-analysis conducted in 3,469 Chinese adults with all types of cancer found the prevalence of anxiety disorders was 49.69 % versus 18.37 % in control subjects (OR = 6.46, 95 % CI = 4.36–9.55, $p=0.000$) (Yang et al. 2013).

In women, there have been several studies concentrating on breast or gynecological cancers. A prospective study of a hospitalized sample of 167 women examined the prevalence of anxiety and depression using the Hospital Anxiety and Depression Scale (HADS-A) and Centre for Epidemiological Studies Depression Scale (CES-D) at diagnosis and again every 8 weeks for 56 weeks. Rates of anxiety (17.7 %), depression (32.5 %) and combined anxiety and depression (35 %) symptoms were highest at diagnosis but dissipated over time and overall rates of anxiety, depression, and combined symptoms were 7.5 %, 23.4 %, and 24.1 %, respectively, at study end, with most improvement having occurred by 24 weeks. Furthermore, using the cut-off for referral to mental health services as ≥11 and ≥16 on the HADS-A and CES-D, respectively, there were 54 % of women who met criteria. Half of these women declined referral, a quarter accepted and a further quarter were already receiving

treatment. This meant that 30 % of women in the study were receiving treatment for a mental health condition and that women were most vulnerable to psychological morbidity at the time of cancer diagnosis (Stafford et al. 2013).

Wurtzen et al. (2013) conducted a randomized controlled trial of an 8-week mindfulness-based group therapy intervention targeting anxiety and depressive symptoms in 336 women with breast cancer. Symptoms were assessed immediately preceding and following the intervention and at 6- and 12-month intervals following thereafter. Intention-to-treat analyses showed differences between groups in levels of anxiety ($p = 0.0002$) and depression (SCL-90r, $p < 0.0001$; CES-D, $p = 0.0367$) after 12 months (Wurtzen et al. 2013).

Gastrointestinal Disorders

Irritable bowel syndrome (IBS) is often associated with anxiety and depression. A sample of 1,077 women found that current diagnosis of irritable bowel syndrome was associated with an increased likelihood of current mood or anxiety disorders with OR = 2.62, 95 % CI = 1.49–4.60. Additionally, half of those participants diagnosed with irritable bowel syndrome IBS had also previously been diagnosed with a mood or anxiety disorder (Mykletun et al. 2010).

Anxiety Across the Life Course in Women

The prevalence of anxiety disorders in women across menstrual cycle, pregnancy, and menopause has been extensively investigated with research revealing rates of some anxiety disorders being higher in postpartum women than in the general population (Ross and McLean 2006). The relationship between the menstrual cycle, menopause, and anxiety disorders has also been considered with links established between hormonal phases of the menstrual cycle and the worsening of anxiety disorders.

Premenstrual Dysphoric Disorder (PMDD)

Premenstrual dysphoric disorder (PMDD) is a mood disorder with onset of functionally impairing or distressing mood symptoms in the late luteal phase of the menstrual cycle. It is classified as a depressive disorder but there are studies which have identified anxiety as a key component (Stein et al. 1989); in particular, the frequency of panic attacks can increase in PMDD (Facchinetti et al. 1992).

Recent research has attempted to interrogate state versus trait symptoms in PMDD and explore the relationship between physiological findings and psychological symptoms. Poromaa (2014) found that in individuals with PMDD, "state" symptoms occur in the luteal phase, suggesting that women with PMDD have altered luteal phase emotion processing and lower pre-pulse inhibition in the late luteal phase, which could reflect

ovarian steroid-influenced altered serotonergic neurotransmission. They suggested that "trait" findings in these women occur in the asymptomatic phases of the menstrual cycle and physiologically exhibited trait vulnerability markers include diminished cardiovascular stress responses, lower P300 amplitude, and lower heart rate variability reflecting increased vagal tone. These findings suggest that women with PMDD share physiological correlates with women with anxiety and depression (Poromaa 2014).

Menopause

A recent systematic review examining 19 studies conducted between 1960 and 2011 (Bryant et al. 2012) evaluated the prevalence of anxiety disorders during the menopausal transition to ascertain whether there was any utility in the diagnosis of "menopausal anxiety" as a discrete category. The review examined the relationship between the vasomotor symptoms of menopause (e.g., "hot flushes"), and anxiety states. Findings suggest that there is no current evidence to suggest that there is an increased prevalence of anxiety disorders during the menopause, nor the emergence of an anxiety disorder specifically determined by the menopause.

Anxiety Disorders During Pregnancy and Postnatally

It has often been considered that pregnancy is a time of low risk for the new onset or exacerbation of an anxiety disorder. However, there is growing evidence that many women suffer from either new onset or worsening of their anxiety disorders during pregnancy. The occurrence of an anxiety disorder in pregnancy has important consequences – it not only impacts on the woman's mental health, but also is a risk for postnatal disorders, as well as having possible effects on the unborn child. Studies of anxiety in a pregnancy show that a not insubstantial proportion of women is affected. For example, Heron et al. (2004) in a large community sample of pregnant women found that 21 % had clinically significant anxiety, and of these 64 % continued to have anxiety postnatally.

Perinatal Post-traumatic Stress Disorder (PTSD)

Perinatal post-traumatic stress disorder (PTSD), that is, PTSD related to medical procedures, childbirth, or other obstetric events, has been reported (Beck 2004). One study found that 20 % of women reported traumatic pregnancy-related procedures, and of these 6 % met criteria for PTSD (Menage 1993). Controversy exists as to whether medical procedures during pregnancy and/or childbirth meet DSM criteria for a traumatic event. While pregnancy and childbirth are not considered to be an event outside the range of normal human experience, the DSM V stressor criterion requires that the person must be exposed to a death, threatened death, actual or threatened serious injury; it is generally acknowledged that traumatic reactions may occur when neither resistance nor escape is possible and helplessness and loss of control are experienced. Childbirth could certainly pose a risk of death and/or serious

injury. Risk factors for perinatal PTSD include previous adverse reproductive events such as ectopic pregnancy, miscarriage, stillbirth, unwanted pregnancy, and abortion; history of sexual trauma (Beck 2004), past traumatic experience (Beck 2004; Menage 1993), prior psychiatric history (Menage 1993), obstetric interventions or complications (Beck 2004; Menage 1993) and poor social support (Beck 2004).

The clinical features of anxiety disorders in pregnancy are similar to those in nonpregnant women. However, concerns over the pregnancy and fetus may present as the predominant feature. For example, in panic disorder, women may interpret panic attacks as something being wrong with the fetus (Weisberg et al. 2002).

Perinatal OCD is classically described as involving obsessive concerns of harming child, together with checking and cleaning compulsions (Abramowitz et al. 2003). It is important to differentiate this from homicidal impulses toward the child (e.g., as part of a psychotic disorder) – in OCD these thoughts are experienced as intrusive and the mother has no wish of harming her child. It has been postulated that these features may be an exacerbation of the normal vigilance toward the child that is characteristic of pregnancy and the postpartum period (Stein and Bouwer 1997).

Women with anxiety disorders also commonly present with numerous physical complaints. Studies of health in pregnancy in women with psychiatric disorders showed an increased frequency of nausea and vomiting (adjusted OR = 2.04, 95 % CI = 1.40–2.98), disability days (OR = 2.10, 95 % CI = 1.49–3.00), and physician visits (OR = 1.52, 95 % CI = 1.10–2.12) in women with anxiety and/or mood disorders (Andersson et al. 2003). Indeed, frequent physical complaints with no discernable physical cause should prompt the clinician to screen for an anxiety disorder.

Risk of Anxiety Disorders in Pregnancy

Maternal Risks

The majority of anxiety disorders in pregnancy have a continued postnatal course. Further, several prospective studies have shown that a prenatal anxiety disorder is one of the strongest risk factors for developing postnatal depression (Milgrom et al. 2008; Sutter-Dallay et al. 2004). An anxiety disorder in pregnancy is thus associated with significant potential maternal morbidity.

Fetal Effects of Maternal Anxiety

Both animal and human studies suggest that antenatal stress/anxiety can cause poorer obstetric outcomes and a range of neurobehavioral problems in exposed infants (Schneider et al. 2002; Bergman et al. 2007). In animals, prenatal stress has been reported to be associated with spontaneous abortion, delays in the birth process, smaller litter size and animals with lower birth weight, compromised physical growth and an increased incidence of malformations (Huizink et al. 2004). Similarly in humans, women reporting high levels of subjective stress have been found to be at doubled risk for delivering preterm or growth-restricted baby (Wadhwa et al.

2002). Antenatal anxiety or stress has been linked with physical defects in the child (Hansen et al. 2000) and low birth weight (Hedegaard et al. 1993). More worryingly, prenatal maternal anxiety has been linked with persisting neurobehavioral problems, including poorer performance on tests of neurodevelopment, increased fearfulness (Bergman et al. 2007) and conduct problems (Huizink et al 2004).

Screening for Anxiety Disorders in Pregnancy

There are no specific screening programs for anxiety disorders in pregnancy. Screening for depression in pregnancy, however, has been well validated and several established screening programs exist (Buist et al. 2002; Austin and Lumley 2003). A strong case can be made to extend these to detect anxiety in pregnancy as well. This is particularly relevant given the rate of women reporting clinically significant anxiety in pregnancy (Heron et al. 2004) and the morbidity that may be associated with the offspring of such women (Glover and O'Connor 2002). In addition, successful management of symptoms present during pregnancy is likely to aid in the reduction of postnatal psychological mood and anxiety disorder (Buist et al. 2002).

The most commonly used screening tool for postnatal depression is the Edinburgh Postnatal Depression Scale (EPDS), referred to as the Edinburgh Depression Scale (EDS) when used during pregnancy (Matthey 2007). It is probable that the EDS also identifies a number of women with anxiety disorders (Matthey 2007). It has been recommended that use of the EDS in combination with a risk questionnaire (assessing alcohol and drug use, partner and social support, and domestic violence) is a good model for screening for both anxiety and depression in pregnancy (Buist et al. 2002; Matthey 2007).

Management of Anxiety Disorders in Pregnancy

Preconceptual Counselling

Ideally, all women known to have an anxiety disorder should have preconception psychoeducation. This should include discussing the risk of relapse during pregnancy and the postnatal period, the risks versus benefits of medications if she were to become pregnant and/or breastfeed as well as a discussion around partner and psychosocial support during pregnancy once baby is born. Asking about the contraception women are using is essential.

Psychotherapy

Psychotherapy is considered first choice for treating mild to moderate anxiety in women who are pregnant. It poses minimal risk to the fetus. While there are no studies addressing the efficacy of psychotherapy in pregnancy, studies in nonpregnant women show efficacy in both interpersonal and cognitive behavioral therapy (CBT).

Relaxation therapy also has shown efficacy in treating anxiety disorders. In a randomized controlled trial of 110 pregnant women with high-level anxiety, 7 weeks of applied relaxation training sessions was associated with significant reductions in low-weight births, cesarean sections, and instrumental extractions (Bastani et al. 2006). Supportive therapy has also been shown to be useful in terms of improving maternal mood and ameliorating anxiety (Fricchione 2004).

Pharmacotherapy

When considering medication in pregnancy, one needs to consider possible effects on the fetus. Two main classes of medication are commonly used to treat anxiety, namely, antidepressants and benzodiazepines.

Selective serotonin reuptake inhibitors (SSRIs) are a first-line pharmacological treatment for anxiety disorders. Large population-based studies have found no increase in the rates of major congenital malformations in infants exposed to SSRIs, with the exception of paroxetine, which has been associated with an increased risk for fetal ventricular and/or atrial septal defects with first-trimester exposure. Paroxetine is consequently best avoided during pregnancy (Källén and Otterblad Olausson 2007).

A concern around SSRI use in pregnancy is the possible increased risk of persistent pulmonary hypertension of the newborn (PPHN), which occurs in 1–2 infants per 1,000 live births. Grigoriadis and colleagues (2014) in a meta-analysis of published studies found that while exposure to SSRIs in early pregnancy was not associated with an increased risk of PPHN (OR = 1.23, 95 % CI = 0.58–2.60; $p = 0.58$), exposure in late pregnancy was (OR = 2.50, 95 % CI =1.32–4.73; $p = 0.005$). One of the strengths of this meta-analysis was the examination of moderator variables which included study design, congenital malformations, and meconium aspiration. The authors were, however, unfortunately not able to assess for the effect of cesarean section, body mass index, or preterm delivery – which are known risk factors for PPHN. It must be noted that even though SSRI exposure in late pregnancy does pose a statistically increased risk of PPHN, the clinical risk remains low, with an estimated 286–351 women needing to be treated to result in an average of one additional case.

It is currently unclear whether SSRI (and other antidepressants) use during pregnancy is associated with an increased risk of autism spectrum disorders. The two largest population-based studies have shown conflicting results (Rai et al. 2013; Hviid et al. 2013). However, both these studies point out multiple confounding factors including the possible effect of depression itself on risk for autism spectrum disorders. Furthermore, Rai et al. (2013) point out that the increased risk of autism spectrum disorders found in their study was very small and must be balanced against the risks of untreated depression.

Infants of women who need to take SSRIs just before delivery can develop toxicity or withdrawal syndromes. Occurrence of either syndrome depends on SSRI half-life, serum concentration, and the pharmacodynamics of other medications given during pregnancy and labor (Sanz et al. 2005). Discontinuation syndromes can

occur within a few hours or days after birth and last up to a month after delivery, depending on the infant's susceptibility. Most suspected SSRI-induced neonatal withdrawal syndromes have been associated with paroxetine, although all SSRIs appear to confer some risk (Sanz et al. 2005). Affected infants are tremulous, jittery, irritable, have poor sucking, high-pitched cries, and sleep and gastrointestinal disturbances.

Tapering and stopping SSRIs prior to the third trimester is an option that would serve to prevent these syndromes and also potentially decrease the risk for PPHN. However, this strategy must be weighed against the risk of relapse if medication is stopped. Benzodiazepine cover may be useful during this period. The antidepressant should be started immediately postdelivery to decrease risk of postpartum relapse. If a withdrawal syndrome is present, breastfeeding may help ameliorate this, by providing smaller regular exposures to SSRIs.

Of the *tricyclic antidepressants* (*TCAs*), clomipramine and imipramine are the most commonly used in the management of anxiety. No increased teratogenic risk has been found with these agents (Nulman et al. 2002). However, due to their adverse side effect profile, particularly postural hypotension, which can be a significant problem in a pregnant patient, and lethality in overdose, they are generally used as second-line agents.

There is little data available on the safety of other antidepressants in pregnancy. A few small studies suggest a slight increased risk of malformations with venlafaxine (Polen et al. 2013) and duloxetine (Hoog et al. 2013), but given the paucity of data non-SSRI antidepressants are probably best used as second- or third-line agents.

There is little data about dosing of antidepressant drugs during pregnancy and the early postpartum period. Some physiologic changes of pregnancy that may lead to altered dose requirements include steroid hormone effects on cytochrome activities (Tanaka 1999); plasma volume expansion; reduction in plasma protein (albumin) levels that leads to decreased drug binding; diminished hepatic blood flow (Stika et al. 2001; Kalra et al. 2005); and increased glomerular filtration rate and renal excretion (Keller et al. 2001; Weinstein 1980). In addition, increases in plasma volume and total body water may increase the volume of distribution and thereby increase the dose requirements that are necessary to sustain therapeutic drug levels (Little 1999).

Heikkinen and colleagues (2002) showed decreasing plasma citalopram concentration after 20 weeks gestation. Sit et al. (2008) replicated this and, in addition, showed this for escitalopram and sertraline, with drug levels decreasing by up to 40 % in some women. Their study also linked decreased plasma levels to changes in mood. The authors suggest that in women whose symptoms recur or worsen a dose increase should be considered.

Benzodiazepines may provide immediate symptomatic relief for anxiety symptoms and can be used alone or in conjunction with an antidepressant for long-term treatment, though the risk of dependence must be considered. Benzodiazepine teratogenicity remains controversial (Levey et al. 2004); some – but not all – data suggest a small but significant increased risk for major malformations/oral cleft malformations with first-trimester benzodiazepine exposure.

Benzodiazepines use close to term can also have fetal effects. Neonatal toxicity ("floppy infant syndrome") – characterized by hypothermia, lethargy, poor respiratory effort, and feeding difficulties – occurs after maternal benzodiazepine use just before delivery (Levey et al. 2004). Neonatal withdrawal may be caused by very late, third-trimester exposure to benzodiazepines. Symptoms – which can persist up to 3 months after delivery – include restlessness, irritability, abnormal sleep patterns, suckling difficulties, growth retardation, hypertonia, hyperreflexia, tremulousness, apnea, diarrhea, and vomiting (Levey et al. 2004; Iqbal et al. 2002). It is not clear though whether this is entirely due to withdrawal per se or whether ongoing exposure via breastmilk plays a role in these symptoms.

When possible, benzodiazepines should be avoided in the first trimester because of possible teratogenicity and then again late in the third trimester before delivery because of neonatal withdrawal syndromes. To minimize neonatal withdrawal, gradually taper the mother's benzodiazepine before delivery (Iqbal et al. 2002). Because the baby's due date is often imprecise, it is sensible to begin this taper 3–4 weeks before the due date and discontinue at least a week before delivery. If benzodiazepines cannot be tapered, it is best to use a short acting agent and to advise the mother to discontinue benzodiazepine use as soon as she thinks she is going into labor. Breastfeeding while taking benzodiazepines is not recommended because of the risk of over-sedating the infant.

Conclusions

Anxiety disorders occur commonly in women. There are differences in the epidemiology, clinical presentation, and etiology between men and women. However, these differences are not yet fully elucidated. In particular, further work is required on how these differences impact on management.

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Anxiety and Related Disorders in Men

Jon E. Grant and Brian L. Odlaug

Introduction

Anxiety disorders are among the most common of all psychiatric disorders. The global current prevalence for anxiety disorders is 7.3 %, suggesting that 1 in 14 people around the world at any given time has an anxiety disorder and 1 in 9 (11.6 %) will experience an anxiety disorder in a given year (Baxter et al. 2013). Per year, the estimated cost (directly and indirectly) of anxiety disorders in the United States alone is over $42 billion (Greenberg et al. 1999). More than 50 % of these expenses are due to clinical care stemming from misdiagnosis, inadequate treatment, and emergency care (including psychiatric and nonpsychiatric hospitalization), the net effect of which is reduced productivity and absenteeism from the workplace (Lepine 2002).

Anxiety disorders have a substantial, negative impact on individuals. Effects are seen not only in emotional and physical health but also through impairments in educational, social, and occupational functioning as well as in overall quality of life (Olatunji et al. 2007). A review of over 1,000 subjects aged 16–25 with anxiety disorders found that those with anxiety disorders had a 5.85 times higher rate of suicide attempts (Boden et al. 2007) than those without an anxiety disorder. There are numerous risk factors implicated in the development of anxiety disorders, including low self-esteem, family history of depression, female sex, childhood sexual abuse, White race, years of education, number of traumatic experiences, and disturbed family environment (Blanco et al. 2014).

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Anxiety disorders are characterized by excessive fear and the associated behavioral disturbances. Although the experience of some degree of anxiety is normal in life, anxiety *disorders* are defined by both the severity and duration of symptoms. In anxiety disorders, the fear is excessive and, in general, lasts for 6 months or longer (APA 2013).

The National Comorbidity Survey found that lifetime prevalence rates for each anxiety disorder were lower in males compared to females: panic disorder (PD) (2.0 % in males vs. 5.0 % females), specific phobia (6.7 % vs. 15.7 %), social anxiety disorder (SAD) (11.1 % vs. 15.5 %), and generalized anxiety disorder (GAD) (3.6 % vs. 6.6 %) (McLean et al. 2011). Because each of the anxiety disorders occur approximately half as commonly in men (APA 2013; Blanco et al. 2014; Mondin et al. 2013; Kessler et al. 2005a), and because the anxiety disorders may differentially impact men (Grant and Potenza 2007), the goal of this chapter is to discuss the role of gender in our understanding and treating of anxiety disorders. Specifically, we will be discussing the impact of gender on social anxiety disorder, panic disorder, generalized anxiety disorder, and phobias, with particular emphasis on their epidemiology, etiology, clinical presentation, current treatment guidelines, and future directions for research.

Social Anxiety Disorder

Social anxiety disorder (SAD), also referred as social phobia, is the fourth most commonly diagnosed psychiatric disorder with lifetime and current prevalence rates of 12.1 % and 6.8 %, respectively, in the general population (Magee et al. 1996; Kessler et al. 2005a, b). SAD appears to be less common in men (11.1 %) than women (15.5 %) (Kessler et al. 1994, 1998). Generally, SAD begins in the early teen years and maintains a chronic course (Bruce et al. 2005; Wittchen and Beloch 1996). Because individuals with SAD experience anxiety and fear in social situations, many also report reduced quality of life in personal and professional areas (Wittchen et al. 1999).

Although the symptoms of SAD do not appear to differ based on gender, the contexts that elicit anxiety may. Men with SAD, for example, tend to have less severe symptoms than women (Turk et al. 1998) and tend to report less distress from public speaking, talking to strangers, and meeting new people (Turk et al. 1998). In addition, and while depression, alcohol dependence, and other anxiety disorders have been documented in people with SAD (Bruce et al. 2005; Grant et al. 2005; Lecrubier and Weiller 1997), the type of psychiatric comorbidity may differ based upon gender (Grant et al. 2005). Studies of adults have found that males with social phobia are less likely to endorse drug use (Buckner et al. 2008; Magee et al. 1996). Among adolescent boys with social phobia, however, the use of nicotine and drugs are more likely (Wu et al. 2010). These findings suggest that the nature of social phobia's relationship with gender and drug use may change during the transition from adolescence to adulthood.

Overall, there is accumulating evidence that abnormal conditioning (e.g., stimulus overgeneralization) and/or extinction failure may contribute to the genesis of social phobias in humans. Abnormalities in conditioning and extinction processes suggest dysfunction within cortico-limbic circuits (Davidson et al. 2000). For example, there is pathophysiological evidence of delayed extinction of the conditioned response in SAD patients relative to controls, supporting the concept that extinction failure could contribute to the maintenance of social fears in SAD patients (Hermann et al. 2002). Based on this hypothesized etiology, why this problem should be less pronounced in males is not yet clear although many hypotheses have been suggested (for a review, see Bekker and van Mens-Verhulst 2007).

Treatment

Psychological Treatments

Cognitive behavioral therapy (CBT) is an evidence-based psychotherapy for individuals with anxiety disorders (Hoffman and Smits 2008; Acarturk et al. 2008) and in particular, SAD (Rodebaugh et al. 2004). CBT involves strategically and repeatedly practicing changing maladaptive behaviors and thoughts by using graded exposure to feared situations, applied relaxation (AR), cognitive restructuring, and learning social skills. Research has demonstrated that CBT is effective in reducing SAD symptomology and may be associated with lower relapse rates (17 %) than pharmacotherapy alone, which has demonstrated relapse rates of 30–60 % in a number of studies (Rodebaugh et al. 2004; Liebowitz 1999). In addition, meta-analyses have suggested that group CBT and individual CBT yield similar treatment results (Rodebaugh et al. 2004; Manassis et al. 2002; Liber et al. 2008) (but see Canton et al. 2012; Mortberg et al. 2007; Stanger et al. 2003). The available data suggest that men and women are equally likely to seek treatment for SAD (Iza et al. 2013) and appear to respond equally well to CBT (Canton et al. 2012).

Pharmacological Treatment

Convincing anxious individuals to consider treatment with psychotropic medications is often quite challenging and may be at least partially responsible for the chronicity of SAD. It requires significant discussions regarding medication-related side effects such as sexual dysfunction, weight gain, and suicidal thinking (McLeod et al. 2004). Pharmacotherapy for SAD includes a variety of medication classes such as selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), anticonvulsants, benzodiazepines, and beta-blockers (for a review, see Ipser et al. 2008).

SSRI medications such as sertraline and paroxetine are Food and Drug Administration (FDA)-approved treatments for SAD, as is the SNRI, venlafaxine, and are considered the first-line medication treatments for SAD (Schneier 2006).

Several randomized, controlled studies have been conducting and reporting the efficacy of these medications (including other SSRIs) for SAD (Wagner et al. 2004; Lader et al. 2004). In general, an adequate clinical trial (8–12 weeks) should be conducted before considering switching to other medications in the same class. Following stabilization, medications should generally be maintained for 12–18 months prior to discontinuation or dose tapering (Schneier 2006). In addition, due to their potential for abuse, benzodiazepines should be prescribed with caution to those with histories of substance abuse. MAOI drugs should be considered as third-line agents for SAD, but may be limited in their acceptability because of the restrictions of the low-tyramine diet. Studies that have examined the differential response to these medications based on gender have found that men and women respond equally well to medications (Van Ameringen et al. 2004).

Panic Disorder

Epidemiological data suggest that panic disorder (PD) has lifetime rates of 3.5–4.7 % and current rates of 2.2–2.7 % in the general population (Kessler et al. 2005a, b; Grant et al. 2005). Men are two times less likely to be diagnosed with PD compared to women (Eaton et al. 1994), but men and women with PD are equally likely to seek treatment (Mackenzie et al. 2012). Both men and women with PD often are usually seen in medical settings prior to seeking psychiatric care and have more frequent visits to emergency rooms compared to patients with other anxiety disorders (Deacon et al. 2008). Complaints of general fatigue, low productivity, and pain are often associated with PD, subsequently masking the disorder, and often result in underdiagnosis by treating physicians (Zastrow et al. 2008). Men with PD are less likely to have respiratory symptoms and faintness during panic attacks (Weissman, 1993).

Co-occurring psychiatric conditions are extremely common in individuals with PD. Studies have found high rates of comorbid anxiety (66–93.6 %), mood (50–73.3 %), impulse control (47–59.5 %), nicotine dependence, and other substance use (27–37.3 %) disorders in patients diagnosed with PD (Kessler et al. 2006; Goodwin et al. 2012). Men with panic disorder, however, may be at lower risk of having a pattern of binge drinking than women (Chou et al. 2011). The poor quality of life secondary to PD is comparable to that reported by patients with major depressive disorder (Candilis et al. 1999), and panic symptoms increase the likelihood of both suicidal ideation and suicide attempts independent of gender (Katz et al. 2011).

Two possible genetic variables associated with PD involve brain-derived neurotrophic factor (BDNF), a protein hypothesized to limit or repair the damage caused by stress, and catechol-*O*-methyltransferase (COMT) (Domschke et al. 2007), both of which has been investigated as the typical gene polymorphisms related to PD. These genetic variables may differ based on gender. One study reported that in male subjects, BDNF Val/Val homozygotes showed a greater increase in salivary cortisol than Val/Met heterozygotes, but in female subjects, the opposite trend was observed (Shalev et al. 2009). Other research suggests

that gender plays a role in the relationship between the COMT gene and anxiety phenotypes (Harrison and Tunbridge 2008). Thus, there is the possibility of BDNF–COMT–gender involvement in anxiety traits and PD. Gender differences may interact with the effects of BDNF and COMT genes on anxiety sensitivity and related personality characteristics in the pathogenesis of this disorder through the monoamine system comprised of serotonergic, norepinephrine, and dopaminergic systems (Konishi et al. 2014).

Treatment

Psychological Treatment

Cognitive behavioral therapy (CBT), which involves psychoeducation, skills for coping with and monitoring panic attacks, cognitive restructuring, and in vivo exposure, has been shown to be an effective treatment for PD. Both individual and group CBT have been demonstrated as useful in reducing the symptoms of PD (El Alaoui et al. 2013). Using meta-analytic techniques on 124 articles, Mitte (2005) examined the efficacy of CBT treatment for subjects with PD with and without agoraphobia, finding an effect size of 0.87 for CBT compared to wait list on measures of anxiety. Other studies have further supported the efficacy of CBT, and found that briefer versions of CBT or CBT with minimal therapist involvement have also been effective (Roberge et al. 2008; Choi et al. 2005). For a recent review of psychosocial treatments for PD, see Otte (2011). There is currently no data to support the view that gender plays a role in response to CBT.

Pharmacotherapy

Two SSRIs, paroxetine and sertraline, have been approved by the FDA to treat PD; however, case studies have shown that other SSRIs may also be beneficial (Goddard and Charney 1998; Sheehan 1999). Other medications to consider are SNRIs (venlafaxine) (Sheehan 2002), tricyclic antidepressants (TCAs) (Zitrin et al. 1983; Andersch et al. 1991; Schweizer et al. 1993), or benzodiazepines (alone or in conjunction with antidepressants or CBT) (Nardi et al. 2013). In addition, the combination of an SSRI or imipramine with CBT (Barlow et al. 2000; Coupland 2008; Marchand et al. 2008; Furukawa et al. 2006), TCAs with CBT (Furukawa et al. 2006), SSRI or SNRI medications with CBT (Craske et al. 2005; Roy-Byrne et al. 2005), and benzodiazepines with exposure therapy (Marks et al. 1993; Cottraux et al. 1995) have all been shown to be beneficial for PD subjects in reducing anxiety and fear associated with the disorder (for a recent review, see Stein et al. 2010). Although early research suggested that men experienced a slightly lower level of response to pharmacotherapy (Yonkers et al. 1998), pooled data analyses have not supported that finding (Pollack et al. 2000; Roy-Byrne et al. 2003).

Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) is a syndrome characterized by excessive and constant worry over different life areas (APA 2013). The 1-year prevalence rate among the general population is approximately 1.6–3 % with a lifetime prevalence of 5.1–6 % (Kessler et al. 2005a). Even though the mean age onset of GAD is in the mid-30s, it is a condition that affects all age groups (Kessler et al. 2001). GAD is about half as common in men compared to women (Vesga-López et al. 2008) with 12-month prevalence rates of 2.4 % for men and 5 % for women (Wittchen et al. 1994).

A majority of individuals with GAD do not seek treatment from a psychiatrist, but instead are seen by primary care physicians (Bélanger et al. 2005), cardiologists, and pulmonologists due to the physical symptoms often associated with the disorder. In fact, men with GAD are less likely to seek treatment for the disorder compared to women (Brawman-Mintzer et al. 1993). GAD is associated with considerable health care costs, lower work productivity, and high utilization of medical resources (Roy-Byrne et al. 2008; Hoffman et al. 2008). Men with GAD, however, report less functional impairment than women (Yonkers et al. 1996). Men with GAD also have a later onset of the disorder, generally have milder symptom presentation, and are at a lower risk of suicide (Steiner et al. 2005; Bruce et al. 2005; Yonkers et al. 1996). Men are also more likely to have comorbid alcohol or drug use disorders, including nicotine dependence while women are more likely to have co-occurring mood or anxiety disorders and having a family history of depression (Vesga-López et al. 2008).

There are several different biological models, which have been implicated in the pathogenesis of GAD. One proposed theory is the behavioral inhibition model (Gray 1988), which involves the septohippocampal area, locus ceruleus, and median raphe nuclei in the brain. This model asserts that during acute stress and fear states, the hippocampus is placed on "high alert" by neurochemicals like norepinephrine and serotonin. Researchers have found that repeated activation of this area leads to hypervigilance and a chronic state of fear in the animals (Vianna et al. 2004). Other proposed models such as the developmental vulnerability model hypothesize that the neurobiological impact of early life stressors may lead to the upregulation of CRF and the HPA axis (Nemeroff 2004). Abnormal noradrenergic, serotonergic, and GABAergic functioning occurs in patients with GAD (Jetty et al. 2001). Another model suggests that vasopressin also plays a role in anxiety and affective disorders, and that antagonism of vasopressin reduces anxiety symptoms (Surget and Belzung 2008).

Functional MRI studies have shown that individuals with GAD demonstrate differential activation patterns in the regions of the amygdala, ventrolateral prefrontal cortex, and anterior cingulate cortex in response to anxiety-inducing negative images compared with healthy controls, and volumetric studies have reported that individuals with GAD show a significant increase in gray matter volumes of the amygdala and dorsomedial prefrontal cortex compared with healthy controls (Monk et al. 2008; McClure et al. 2011; Schienle et al. 2011). More recently, a study showed that men with GAD exhibited a significant decrease in the volume of the dorsolateral prefrontal cortex relative to women (Moon et al. 2014).

Treatment

Psychotherapy

Psychotherapy, such as CBT and applied relaxation (AR) therapy, has a strong evidence base for the treatment of GAD (Gorman 2003; Canadian Psychiatric Association 2006; Hunot et al. 2007; Cuijpers et al. 2014). One meta-analysis (Hunot et al. 2007) examined 13 studies comparing CBT to treatment as usual/wait list (TAU/WT) and found that a significantly higher percentage (47 % vs. 13 %) of subjects in the CBT group responded to treatment. In addition, applied relaxation (AR) is another form of therapy that has shown benefit in the treatment of GAD (Cuijpers et al. 2014). In AR, patients learn progressive relaxation techniques, how to identify feared situations and utilize relaxation skills in stressful situations (Arntz 2003). Studies that have compared CBT to AR have found that both treatments are comparable in decreasing anxiety and depression (Ost and Breitholtz 2000; Borkovec and Costello 1993). There is no evidence that men respond differently to CBT or AR compared to women.

Pharmacotherapy

To date, there have been eight different medications that have been approved by the FDA for the treatment of GAD, including SSRIs (paroxetine, escitalopram), SNRIs (duloxetine, venlafaxine), benzodiazepines (diazepam, lorazepam, alprazolam), and azapirone (buspirone). A meta-analysis of 39 pharmacotherapy interventions revealed an overall effect size of 0.60 for medication treatment of GAD (Gould et al. 1997). SSRIs are widely considered to be the first-line treatments for GAD (Pollack et al. 2001; Davidson et al. 2004). In terms of a differential response based on gender, the limited research suggests that men may be less likely to respond to venlafaxine, more likely to respond to fluoxetine, and equally likely to respond to sertraline compared to women (Pollack et al. 2003; Steiner et al. 2006; Simon et al. 2006).

Specific Phobias

Specific phobias are characterized by fear or anxiety that is circumscribed to the presence of a particular situation or object and the response is not the same as a normal, transient fear that may commonly occur in the population. The fear must be intense or severe (APA 2013). Specific phobias may encompass a range of objects or situations that induce fear –high places (e.g., acrophobia), certain animals (e.g., spiders), and health-related issues (e.g.,blood, needles).

Specific phobia is one of the most common mental health disorders with a lifetime prevalence of 9.4–12.5 % and a 12-month prevalence of 7.1–8.7 % (Kessler et al. 2005a; Stinson et al. 2007). Men have half the lifetime risk for specific phobia compared to women (12 % vs. 26 %) (Fredrickson et al. 1996). The mean age at

onset of specific phobia is generally 9–10 years, with a mean duration of 20 years (Stinson et al. 2007). Among adolescents, however, this gender discrepancy appears to apply only to those who are affected with a greater number of phobia types (Burstein et al. 2012).

In terms of clinical presentation, men are less likely to report situational or animal phobias and are less likely to have multiple phobias (Fredrickson et al. 1996). Women with specific phobia appear to be at increased risk (twofold increase) of developing other anxiety disorders, depression, and somatoform disorders (Trumpf et al. 2010).

Twin studies suggest a genetic influence in the development of specific phobias. Situational and medical phobias may have a lower heritability among men but animal phobias appear equally heritable by men and women (Kendler et al. 2002).

A recent review found that functional neuroimaging, mostly using symptom provocation paradigms, has demonstrated abnormal activations in brain areas involved in emotional perception and early amplification, mainly the amygdala, anterior cingulate cortex, thalamus, and insula. The insula, thalamus, and other limbic/paralimbic structures are particularly involved in specific phobias with prominent autonomic arousal. Emotional modulation is also impaired after exposure to phobic stimuli, with abnormal activations reported for prefrontal, orbitofrontal, and visual cortices (Del Casale et al. 2012).

Treatment

Psychotherapy

Although only 8.0 % of individuals with specific phobia report receiving treatment (Stinson et al. 2007), an analysis of psychotherapy research supports the use of CBT, specifically involving exposure therapy. In fact, *in vivo* exposure therapy for most of the specific phobia types has a response rate of 80–90 % (Choy et al. 2007). In addition, long-term follow-up studies of CBT suggest that treatment gains are generally maintained from 6 months to 1 year, and often improved if self-exposure is continued during the follow-up period (Choy et al. 2007). Men appear to respond as well as women to CBT. A meta-analysis of 33 randomized treatment studies for specific phobias found that exposure-based treatments were effective in reducing symptoms (Wolitzky-Taylor et al. 2008).

Pharmacotherapy

There are limited data regarding effective pharmacotherapy options for specific phobias. One study of paroxetine, an SSRI, showed significant superiority to placebo (Benjamin et al. 2000). Two benzodiazepine studies suggest limited acute use for either flying phobia (Wilhelm and Roth 1997) or dental phobia (Jöhren et al. 2000). Due to the limited research, no useful gender comparisons can be made.

Conclusions/Future Directions

The current research indicates that anxiety disorders, as an overall group of disorders, are less common among men. Etiological factors have been explored in anxiety disorders, yet despite the high occurrence of anxiety disorders globally, the data are currently too limited to determine if men and women with anxiety disorders have different etiologies. In addition, little is known about whether men and women respond differently to available treatment options. Further research is needed to examine if and how gender influences response to treatment. Areas such as neuroimaging (SPECT or fMRI) (Roth 2008), molecular psychiatry, animal models (including translational research) (Glasgow et al. 2005; Roth 2008), innovative clinical trials (Tunis et al. 2003), pharmacogenetics (Broich and Möller 2008), and refining different modes of psychotherapy and combining them with pharmacological interventions (Hyland 1991; Foa et al. 2002) are all beneficial in learning more about the role of gender in these disorders.

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