Chapter 1

Introduction and Conceptual Overview

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Introduction

Historically, clinicians and researchers interested in the mental health of older people have focused on depression and dementia and have given little attention to anxiety except as a complication of depression or dementia. Over recent years, however, research into anxiety in older people has increased substantially, leading to both a burgeoning scientific literature and increasing clinical interest in the field.

In this book, expert clinicians and researchers combine to provide readers with a detailed and scholarly overview of current knowledge in relation to anxiety in older people. They also highlight gaps in both theory and practice, pointing the way forward. Before introducing each chapter, we will provide a brief conceptual overview of anxiety in older people to set the scene for the rest of the book.

Conceptual Overview

Naturalist Charles Darwin noted that fear and anxiety are phylogenetically ancient emotions that confer a survival advantage across species (Darwin, 1872). These emotions facilitate escape from immediate danger and prepare the individual to respond to future threat. Although a moderate level of anxiety may be adaptive and may even improve performance (Yerkes & Dodson, 1908), high and prolonged levels of anxiety are maladaptive and may represent a mental disorder.

Complex brain mechanisms underpin both adaptive and maladaptive responses to threat in humans and other animals. While the prefrontal cortex is involved in social cognition and threat appraisal, the limbic system is most involved in generating fear and anxiety responses. Neuroimaging studies with both functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have confirmed the existence of fear-related circuits involving the amygdala, insula, and anterior cingulate (Sehlmeyer et al., 2009). Studies in rodents have shown that the amygdala is critical to the generation of panic, and fear responses in the amygdala are difficult to extinguish (Sah & Westbrook, 2008). The hippocampus modulates stress responses through the hypothalamic–pituitary–adrenal (HPA) axis, and there is evidence that individuals with greater hippocampal volume and neurogenesis have greater resilience to stress (Martin et al., 2009).

Although no genes of large effect have been discovered in this area, studies in twins indicate that about 30–40% of the variation in risk of anxiety disorder is of genetic origin (Norrholm & Ressler, 2009) and that genetic mechanisms may play a larger role in panic disorder than in generalized anxiety disorder (GAD). Genetic factors continue to play an

important role in late-life anxiety (Gillespie et al., 2004), and epigenetic mechanisms may also play a part (Gottschalk & Domschke, 2016).

Early-life experiences appear to be critical to the development of adult anxiety, and studies in rodents confirm this view. Rat pups separated from their mothers for relatively short periods of time during the early postnatal period demonstrate increased anxiety-related behaviours as adults (Kalinichev et al., 2002). In humans, childhood abuse has a persisting effect on the risk of late-life anxiety (Cougle et al., 2010), and this may be mediated through dysregulation of the negative feedback system of the HPA axis (Lähdepuro et al., 2019; Lupien et al., 2009). In adult life, adverse life events are also associated with new-onset anxiety disorders (Miloyan et al., 2018).

Until recently, the anxiety disorders were considered to include GAD, social anxiety disorder, panic disorder, agoraphobia, simple phobia, post-traumatic stress disorder (PTSD), obsessive–compulsive disorder (OCD), adjustment disorder with anxiety, and a group of organic and substance-related anxiety states. However, since the publication of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) (American Psychiatric Association, 2013), the nosological status of PTSD and OCD has changed. These disorders have been assigned new categories separate from the anxiety disorders.

In DSM-5, PTSD is included in a chapter labelled 'Trauma- and Stressor-Related Disorders', and in the International Classification of Diseases, 10th Revision (ICD-10) (World Health Organization, 1992), it is included in a chapter labelled 'Reaction to Severe Stress, and Adjustment Disorders'. In both taxonomies, acute stress reactions and adjustment disorders are now in the same section as PTSD. ICD-10 includes this section under the broader rubric of 'Neurotic, Stress-Related and Somatoform Disorders' with the codes F40–F48.

The splitting off of stress-related disorders, including PTSD, from the anxiety disorders in contemporary nosologies may provide a measure of conceptual clarity for some clinicians and insurers, but this makes less sense from an aetiological perspective. It is clear that adverse life events, whether experienced in childhood or adulthood, are associated with the onset of many different psychiatric disorders, including anxiety disorders.

Placement of OCD in its own chapter in DSM-5 brings the American nosology in line with ICD-10. OCD shares a chapter on 'Obsessive-Compulsive and Related Disorders' with 'Body Dysmorphic Disorder', 'Hoarding Disorder', and a variety of other conditions, as recommended by commentators (e.g., Stein et al., 2010)

Certain personality traits, especially neuroticism and conscientiousness, predispose individuals to the development of anxiety symptoms and anxiety disorders (Rosellini & Brown, 2011), and about one-third of the genetic influence on GAD is shared with neuroticism (Mackintosh et al., 2006). In people with dementia due to probable Alzheimer's disease, informant-rated premorbid neuroticism is associated with current anxiety measured on the Neuropsychiatric Inventory (Archer et al., 2007). Neuroticism has been found to increase with age in cognitively normal older people who have a positive amyloid PET scan and are at increased risk of future dementia due to Alzheimer's disease (Fredericks et al., 2018).

Anxiety, at least when it is experienced as fear or worry, is scalable and lends itself to dimensional thinking. This is helpful for researchers, but it is of less utility when clinicians are dealing with third-party payers, who generally require a categorical diagnosis rather than a scale score. As a consequence, there is tension between dimensional measurement and categorical assignment when thinking about anxiety symptoms and anxiety disorders.

DSM-5 has attempted to deal with this by requiring a certain number of symptoms over a certain period of time, together with impairment of social or occupational function, before a categorical diagnosis can be made. The construction of syndromes in this way aids clinical case formulation, communication with patients and between clinicians, and planning of therapeutic interventions, but it does little to assist scientific enquiry into causal mechanisms.

Existing diagnostic criteria for anxiety disorders do not provide for age-related variations in aetiology, clinical presentation, or course. This leaves open the possibility that the epidemiology of anxiety disorders in older adults has been biased by the use of criteria better suited to use in younger people or in early-onset cases rather than in older people or in late-onset cases. In keeping with this concern, there is evidence that sub-threshold cases of anxiety make up a larger proportion of clinically significant cases in older people (Grenier et al., 2011; Miloyan et al., 2015).

It is instructive to consider the burden of disease due to anxiety disorders. Burden is measured using estimates of years lived with disability (YLDs) and years of life lost (YLLs) due to premature mortality. Disability-adjusted life years (DALYs) represent the sum of YLDs and YLLs. Mental disorders are responsible for 22.9% of global YLDs and 7.4% of global YLLs (Whiteford et al., 2015). Among mental disorders, anxiety disorders are second only to major depressive disorder in terms of global DALYs. There is a greater global burden due to anxiety disorders than due to schizophrenia and bipolar disorder. In 2010, anxiety disorders accounted for 10.4% of the global burden due to mental, neurological, and substance use disorders when measured in DALYs (Whiteford et al., 2015). The burden associated with anxiety disorders differs markedly between individuals; it is higher among women and young people than among men and older people (Baxter et al., 2014). Burden associated with anxiety disorders also varies considerably between countries or regions. Burden due to anxiety disorders is highest in North Africa/the Middle East and North America and lowest in East Asia and Eastern Europe (Baxter et al., 2014). Burden also varies by age. Among adult men and women, the global burden associated with anxiety disorders is highest among those aged 20–34 years and lowest among those aged 75 years and over (Baxter et al., 2014).

The available epidemiological data, albeit mostly from developed countries, indicate that anxiety symptoms and anxiety disorders decline in prevalence after the age of about 50 years (Byrne, 2020). This decline in prevalence occurs in parallel with a decline in trait neuroticism. However, most of the available evidence also suggests that the prevalence of anxiety increases in people with mild cognitive impairment and dementia. Anxiety has conventionally been considered to be a reaction to cognitive impairment, but anxiety has also been postulated as a potential cause of dementia (Gulpers et al., 2016).

Anxiety disorders as they are currently understood exhibit considerable co-morbidity with other anxiety disorders. This means that individuals often meet diagnostic criteria for more than one anxiety disorder at the same time. For example, in the National Epidemiologic Survey on Alcohol and Related Conditions – III (NESARC-III) population survey of the USA (Grant et al., 2014), in which 5,806 individuals aged 65 years and over were sampled, 658 (11.3%) older people met draft DSM-5 diagnostic criteria for an anxiety disorder in the past year. Of these, 126 met criteria for more than one anxiety disorder in the past year. Thus, 19.1% of older people with an anxiety disorder (or 2.2% of the general US population of older people) met criteria for more than one current anxiety disorder.

Anxiety disorders also exhibit co-morbidity with other mental disorders. In the NESARC-III survey, 387 (6.7%) older people met diagnostic criteria for major depression in the past year. Of these, 141 (36.4%) also met diagnostic criteria for one or more anxiety disorders in the past year. Conversely, 21.4% of those with a past-year anxiety disorder met criteria for a past-year major depressive episode. The anxiety disorders most often associated with major depression were GAD, PTSD, specific phobia, and social anxiety disorder.

In the NESARC-III survey, 139 (2.4%) older people met criteria for past-year alcohol use disorder. Of these, 26 (18.7%) also met criteria for one or more past-year anxiety disorders. Conversely, of 658 older people with past-year anxiety disorder, 4% had a co-morbid past-year history of alcohol use disorder. The anxiety disorders most often associated with alcohol use disorder were GAD, PTSD, social anxiety disorder, and specific phobia.

Anxiety disorders generally have their onset in young and middle-aged people. In the Australian National Survey of Mental Health and Wellbeing 2007, the median age of onset for GAD was 26 years. Only 10% of cases of GAD had their onset after the age of 60 years (Gonçalves & Byrne, 2012). However, when anxiety disorders have their onset in later life, they may be markers for undiagnosed cognitive impairment or incipient dementia.

The search for risk factors for incident anxiety disorders in later life requires adequately powered prospective studies. Such studies are uncommon due to their high cost and the natural attrition of older people. Findings from the small number of available prospective studies are conflicting (e.g., see Chou et al., 2011; Zhang et al., 2015). More work is needed.

There has been considerable recent activity in the development of anxiety rating scales for use in older people. This has been important because the Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959) and the Beck Anxiety Inventory (BAI; Beck et al., 1988) have generally been considered inappropriate for use in older people because they are both dominated by somatic items, assessment of which can be confounded by the symptoms of general medical conditions that become more prevalent with advancing age. More recently, several scales have been developed specifically for use in older people. These include the 10-item Self-rated Anxiety Screening Test (SAST; Sinoff et al., 1999) designed for use in geriatric medicine settings, the 20-item self-rated Geriatric Anxiety Inventory (GAI; Pachana et al., 2007) designed for the self-assessment of generalized anxiety, the 30-item self-rated Geriatric Anxiety Scale (GAS; Segal et al., 2010), and the 18-item clinician-rated Rating Anxiety in Dementia instrument (RAID; Shankar et al., 1999). The GAI is available in a 5-item short form (GAI-SF; Byrne & Pachana, 2011) and the GAS is available in a 10-item form (GAS-10; Mueller et al., 2015). Several of these scales are available in multiple languages. Further work is needed in examining the performance of anxiety rating scales in the context of disabling physical illness and cognitive impairment.

The study of treatment interventions for anxiety disorders in older people is a relatively underdeveloped field. Conventional interventions for anxiety disorders in older people include the development of a therapeutic alliance, psychoeducation about the nature of anxiety and its treatment, lifestyle modification including stimulant reduction, sleep hygiene, physical exercise, relaxation training, behavioural activation, non-specific and specific exposure, formal psychotherapy including cognitive behaviour therapy (CBT), and antidepressant medication. Whilst conventional treatments delivered by trained clinicians are moderately effective (e.g., Gonçalves & Byrne, 2012), there are major problems with treatment accessibility for many older people. To date, most treatment outcome data in older people have been for GAD in cognitively intact individuals. There is a need for clinical trials in other anxiety disorders in later life and for clinical trials for anxiety disorders in the

context of cognitive impairment and dementia. It is encouraging to see that work is being done to adapt psychotherapy for older people with Parkinson's disease, a neurodegenerative disorder commonly associated with anxiety (Dissanayaka et al., 2016; Knight et al., 2016).

The development of new and more effective biological treatments is likely to be predicated upon advances in the basic neuroscience of anxiety. In the absence of such advances, clinical trial work is likely to be limited to currently available psychotropic medications and the repurposing of drugs used for other disorders. Sophisticated laboratory techniques, including the use of optogenetics in living mice, have demonstrated the ability to turn anxiety circuits on and off (Tye et al., 2011). The search for molecular mechanisms underpinning anxiety and stress-related disorders is in its infancy, but one possibility is cAMP-specific 3′,5′-cyclic phosphodiesterase 4B, an enzyme that in humans is encoded by the *PDE4B* gene (Meier et al., 2019). *PDE4B* is also involved in memory and long-term plasticity in rodents, providing a potential mechanism by which anxiety and memory are linked. It is thus likely that our knowledge of the basic biological mechanisms underpinning anxiety will advance rapidly. We look forward to the translation of these laboratory findings into treatments for humans.

Research into psychosocial treatments for late-life anxiety has both a shorter history and arguably a lower success rate than research targeting depression in later life. For example, for GAD in later life, a meta-analysis of studies demonstrated CBT to be superior to wait-list or 'treatment-as-usual' conditions, but not to active controls such as supportive counselling (Hall et al., 2016). Other interventions, such as those using mindfulness, have received mixed support and require further studies with better control conditions (Geiger et al., 2016). Translations of findings from clinical trials of psychosocial as well as combination therapy using psychosocial interventions with pharmacotherapy have suffered from the inclusion of participants under age 65, a lack of data on the growing demographic segment of those over age 75, and a paucity of studies targeting co-morbid depression and anxiety in older persons – a relatively common clinical presentation (Moller et al., 2016). Technological innovations have opened up the possibility of anxiety treatments within a 'virtual reality' setting (e.g., Meyerbröker & Emmelkamp, 2014); these are a promising new approach for specific phobias.

Chapter Summary

The first chapters of the text deal with broader aspects of anxiety disorders. In Chapter 2, Byrne and Pachana address the epidemiology of anxiety disorders in older people. They discuss likely sources of variation in population estimates and consider both prevalent and incident anxiety disorders. They highlight conflicting findings in relation to risk factors for anxiety disorders in older people. In Chapter 3, Bryant discusses diagnostic issues in late-life anxiety. She considers the value of diagnosis as well as its limitations. In Chapter 4, Grenier and Richer deal with sub-threshold anxiety in later life. They note its high prevalence and association with insomnia, impaired daily functioning, suicidality, and increased use of health services. They highlight inconsistent findings in the scientific literature about the temporal stability of sub-threshold anxiety. They discuss the relationship of anxiety to depression and to several important physical disorders, as well as treatment implications.

Cultural issues are not raised often enough in discussions of anxiety. In Chapter 5, Lin and Hosseini address cross-cultural issues in late-life anxiety. They note conceptual differences between Western and non-Western cultures in the perception of anxiety, including non-Western holistic models in which the distinction between physical and mental health is

not as strongly demarcated. They caution that much cross-cultural research into anxiety has been undertaken in immigrants and may not generalize well to their countries of origin. They note that, in some cultures, the notion of mental illness refers to serious but low-prevalence mental disorders such as schizophrenia and bipolar disorder, rather than to high-prevalence disorders such as anxiety and depression.

The following chapters address assessment as well as the cognitive sequelae of anxiety. In Chapter 6, Gould, Kok, Ma, and Edelstein discuss the clinical assessment of late-life anxiety. They note common differences between the clinical presentation of anxiety in older and younger people. They provide useful overviews of the properties of the diagnostic interviews and rating scales that might be used in the assessment of older people with anxiety problems. They deal with specific issues including the assessment of anxiety in the presence of physical illness. In Chapter 7, Bower and Wetherell address attention bias in older people with anxiety and co-morbid depression. They indicate that biased attention to negative information is a core component of cognitive models of anxiety and depression. They discuss the interference effect of negative information for anxious older people and report evidence from fMRI studies of failure of the dorsolateral prefrontal cortex to dampen down the amygdala in older people with GAD. In Chapter 8, Beaudreau, Petkus, Hantke, and Gould address anxiety and cognitive function. They note that older adults with anxiety symptoms exhibit poorer performance on global measures of cognitive functioning. They also note that anxiety in older people is a predictor of future cognitive decline and dementia. They discuss cognitive and biological models that may account for the link between anxiety and cognitive function.

Therapeutic interventions across a variety of settings and specific disorders is the focus of the following chapters. In Chapter 9, Dissanayaka addresses anxiety in Parkinson's disease. She emphasizes the specific nature of anxiety in this progressive neurodegenerative disorder, which often has its onset in later life. She deals in detail with putative biological underpinnings and therapeutic interventions. In Chapter 10, Shead, Rodriguez, Dreeben, and McBride deal with anxiety in older adults across various care settings, including home care, long-term care, and palliative care. They discuss the challenges of assessment and management in these diverse settings. In Chapter 11, Ramos and Stanley detail the role of psychosocial interventions in the treatment of anxiety in later life. They note that CBT is effective for late-life GAD when compared with wait-list controls, minimal contact, or treatment as usual, but not when compared with other active interventions. However, they indicate that CBT has efficacy as an augmentation strategy in older people with GAD treated with antidepressant medication. They suggest that relaxation training and other behavioural approaches may be preferable to cognitive skills acquisition, particularly in the context of memory impairment. They discuss modification to standard techniques for use with older people with cognitive or sensory changes. They discuss psychosocial interventions in several specific situations, including hoarding and fear of falling. They also discuss novel modes of delivery of psychosocial interventions. In Chapter 12, Byrne addresses the role of psychotropic medication in the management of anxiety disorders. He notes that if medication is to be used, antidepressants are preferred. He summarizes the evidence from clinical trials for the use of antidepressants and several other classes of psychotropic medication. He notes that most of the clinical trial evidence in older people has been obtained from studies of short duration and relates to the treatment of GAD. There is scant evidence for the pharmacological treatment of anxiety disorders other than GAD in older people.

Potential avenues meriting further research are the focus of the final chapters of this text. In Chapter 13, Perumal and Sah discuss the findings from recent animal models in anxiety research. They emphasize the role of the amygdala and its connections with the medial prefrontal cortex and the hippocampus. They show there are different circuits mediating fear learning and extinction. They outline how these findings in laboratory animals could be translated into humans. And finally, in Chapter 14, Pachana and Byrne summarize the field of anxiety disorders in older people, highlight important clinical issues, and make suggestions for future research.

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