# A lifespan view of anxiety disorders

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*Neurodevelopmental changes over the lifespan, from childhood through adulthood into old age, have important implications for the onset, presentation, course, and treatment of anxiety disorders. This article presents data on anxiety disorders as they appear in older adults, as compared with earlier in life. In this article, we focus on aging-related changes in the epidemiology, presentation, and treatment of anxiety disorders. Also, this article describes some of the gaps and limitations in our understanding and suggests research directions that may elucidate the mechanisms of anxiety disorder development later in life. Finally, we describe optimal management of anxiety disorders across the lifespan, in "eight simple steps" for practitioners.*

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## Introduction

Picture the world in 2050. A demographic shift towards older age that began generations ago will have reached its peak, and 2 billion individuals will be aged 60 and older.[1] In the United States and much of Europe, one in three persons will be in this old-age demographic (compared with one in five today). It is increasingly clear that the common mental disorders of emotion— anxiety disorders and unipolar depression—are a terrible scourge across the lifespan: they not only induce significant misery and suffering for the patient and his/her whole family, but with increasing age they become increasingly deleterious to health and cognition, even increasing mortality risk in older adults. Given such deleterious effects, understanding the common mental disorders in this large and growing demographic would seem to be a question of some importance.

The last decade has seen several advances in our knowledge of the epidemiology, course, and treatment of anxiety disorders, and how this changes into old age. Yet, even though anxiety disorders are the most common mental disorders in older adults, there has been scant attention paid to some major issues regarding anxiety disorders in older adults.

In this review, we present a lifespan view of anxiety disorders, primarily from an aging perspective, but also with an examination of the changing picture of anxiety disorders and their treatment throughout the lifespan from childhood to old age. This review will focus on three aspects of anxiety disorders: epidemiology, presentation, and treatment. One of the major arguments that will be advanced is that anxiety disorders are common in older adults and cause considerable distress and functional

impairment, and that, absent improvements in detection and management, geriatric anxiety disorders will become an increasing human and economic burden. We will also argue that much is known already about the optimal management of anxiety disorders across the lifespan into old age, such that practitioners could greatly improve outcomes of their patients with these common problems even now, if they follow eight simple management steps which are outlined.

Additionally, it will be obvious from reading this review that significant gaps remain in our understanding of many aspects of anxiety disorders, particularly in older adults. Throughout the review, we will point out these gaps in our knowledge, and we will finish with a brief prospectus on research that could begin to fill these gaps.

## Epidemiology of anxiety disorders throughout the lifespan

*Table I* shows prevalence estimates from several large epidemiologic studies that focused on elderly persons. As a whole, the studies suggest that generalized anxiety disorder (GAD) is the most common anxiety disorder and is as common, or more common, in older as in younger adults; other anxiety disorders are less common. Several excellent reviews of the epidemiology of late-life anxiety disorders exist[2-4] and we will not recapitulate them, but will note two key and related points from them. First, epidemiologic studies have produced wide variations in prevalence estimates of anxiety disorders in elderly persons. One systematic review found 28 epidemiological studies of anxiety symptoms, or disorders, in older adults: 19 in community samples, and nine in clinical samples. The range of anxiety disorder prevalence estimates in those studies varied markedly, ranging from 1.2% to 15% in community samples and from 1% to 28% in medical settings. The prevalence of clinically significant anxiety symptoms ranges from 15% to 52% in community samples and 15% to 56% in medical settings.[2] Second, anxiety disorders (and symptoms), already difficult to measure accurately in young adults, are more difficult to assess in older adults. In a section below, we will discuss difficulties in the assessment and diagnosis of anxiety disorders and symptoms in older adults and how these might affect prevalence estimates.

## Presentation of anxiety disorders across the lifespan

*Figure 1* portrays our current understanding of how different forms of anxiety disorders may predominate at different stages of the lifespan. Phobias (particularly social and specific phobias) may predominate in childhood; panic disorder and post-traumatic stress disorder (PTSD) may be at their highest prevalence in adulthood; while worry disorders (ie, GAD) may be most common in old age. Anxiety disorders with a strong autonomic nervous system component (eg, resulting in panic attacks or panic-like symptoms) are usually considered to be more common in childhood or early adulthood than

| | Longitudinal Aging Study Amsterdam (LASA)[11] | Epidemiologic Catchment Area (ECA)[227] | Amsterdam Study of the Elderly (AMSTEL)[26] | Australian National Mental Health and Well-being Study (NMHWS)[228] | Canadian Community Health Survey (CCHS)[229] | National Comorbidity Study-Replication (NCS-R)[230] |
|---|---|---|---|---|---|---|
| N | 3107 | 5702 | 4051 | 1792 | 12792 | 1461 |
| Age | 55-85 | 65+ | 65-84 | 65+ | 55+ | 65+ |
| Any anxiety disorder | 10.2% | 5.5% | Not assessed | 4.4% | Not assessed | 7.0% |
| GAD | 7.3% | 1.9%* | 3.2% | 2.4% | Not assessed | 1.2% |
| Any phobia | 3.1% | 4.8% | Not assessed | Not assessed | Not assessed | 4.7%*** |
| Social phobia | Not assessed | Not assessed | Not assessed | 0.6% | 1.3% | 2.3% |
| Agoraphobia | Not assessed | Not assessed | Not assessed | 0.8%** | 0.6% | 0.4% |
| Panic disorder | 1.0% | 0.1% | Not assessed | 0.8%** | 0.8% | 0.7% |
| OCD | 0.6% | 0.8% | Not assessed | 0.1% | Not assessed | Not assessed |
| PTSD | 0.9% | Not assessed | Not assessed | 1.0% | Not assessed | 0.4% |

**Table I.** Prevalence estimates for anxiety disorders in older adults from five community studies. GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; *prevalence estimate of GAD in ECA is from one site only; **prevalence estimate from NMHWS is for panic disorder and/or agoraphobia ; ***prevalence estimate from NCS-R is for specific phobia

later in life, particularly with respect to social phobia and panic disorder. Age-related changes in brain structure or function or peripheral physiology likely reduce the propensity for autonomic responses.[5] Here we note the caveat that specific disorders "may" peak at different times in the lifespan because these data are largely based on epidemiological studies. The difficulty of retrospective evaluation of age of onset of mental disorders is a limitation to this assertion,[6] as is the difficulty of detecting late-onset anxiety disorders using standardized assessment tools that were developed for young adults..[2] Additionally, fear of falling (FOF) is a common and uniquely geriatric syndrome[7] marked by fear and avoidance. High rates of older adults in the community report a FOF,[8] and in its more severe forms the consequences of this fear are very serious, including a curtailing of activities[9]; thus the problem is akin to agoraphobia in the more severe manifestation. However, it appears difficult to diagnose FOF as an anxiety disorder, due in large part to issues with insight and goodness of fit with existing *DSM-IV* nosology.[10] The one anxiety disorder that seems to be more commonly present in late life is GAD.[11]

## Why might anxiety disorders develop late in life?

Although anxiety disorders are properly thought of as neurodevelopmental conditions (ie, they develop in the context of brain changes which occur characteristically at various points in the lifespan), this does not mean that they are of childhood onset only. In fact, anxiety can develop in old age: one study found new-onset anxiety disorders in 11% of older women and 2% of older men.[12]

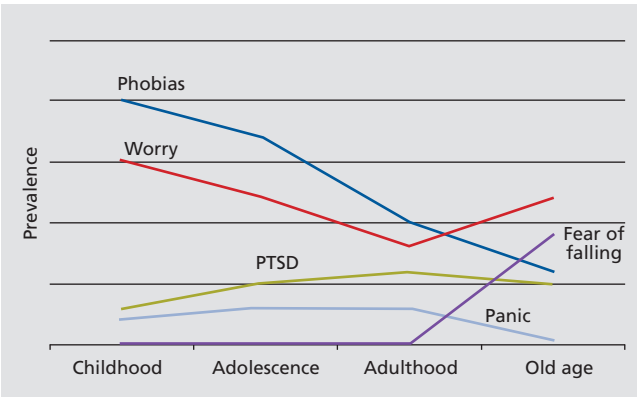


**Figure 1.** Changes in anxiety disorder presentation across the lifespan. PTSD, post-traumatic stress disorder

Up to one half of older patients with GAD have onset later in life.[13-15] A review of European epidemiological studies found that the incidence of agoraphobia may increase over the lifespan in women.[16] While older adults may develop PTSD less frequently after traumatic events than younger adults do,[17] late-onset PTSD is not uncommon.[18-20] Even panic disorder, thought to have a particularly low late-life incidence, has been documented in some studies,[21] particularly in patients with medical illness.[22]

There are potential neurobiological risks for late-onset anxiety disorders (although these have not been subjected to empirical testing). We conceptualize pathological anxiety as potentially due to a functional disconnect between amygdala (and possibly insula) and frontal areas (including anterior cingulate cortex, dorsolateral and ventromedial prefrontal cortex), impairing natural fear extinction and thus converting fears or worries into chronic pathological conditions.[23] This process could be exaggerated in elderly persons, in whom aging and neurodegenerative changes may lead to reduced functional connectivity.[24,25] Late-onset anxiety may thus be conceptualized as a consequence of neurobiological changes in aging involving pathways which are suspects in the onset and chronicity of anxiety disorders.

Psychological and social risk factors also play a role in the development of late-onset anxiety disorders. Some risk factors for geriatric anxiety and depression are shared, eg, female gender, cognitive impairment, chronic health conditions, poor self-rated health, functional limitations, personality traits such as neuroticism, and poor coping skills.[26,27] Additional risk factors for anxiety specifically are being childless, having lower income, and experiencing traumatic events.

These psychosocial and neurobiological changes in aging interact with each other and with predisposition (eg, genetic or early-life adversity) to produce late-onset anxiety disorders. Additionally, age-related protective factors may include social support, religiosity, physical activity, cognitive stimulation, and effective coping skills learned throughout a lifetime. As in childhood disorders, such protective factors may buffer the effects of genetic and other risk factors.

Prospective studies are needed to study these risk and protective factors and their interactions. One option is to conduct a preventive intervention study for late-life anxiety disorders.[28] A preventive intervention study could enroll subjects with one or more of these risk factors, probably those with subsyndromal depressive or

anxiety symptoms, and manage them with a stepped-care approach to prevent the onset of an anxiety disorder.[29] Such a preventive study could gather biological and behavioral data to elucidate biological, psychological, and social variables associated with increased likelihood of developing chronic anxiety. Elucidation of such risk signatures could then lead to a second generation of more robust preventive interventions that could target individuals most likely to benefit from prevention and intervene directly on the modifiable risk.[30] Such research would be consistent with the National Institute of Mental Health's vision of "pre-emptive" and "personalized" mechanistic-based novel intervention development.[31]

## Course

Anxiety disorders are among the most persistent mental health syndromes. The few longitudinal studies that have been carried out in older adults with anxiety suggest that they tend to be persistent in this age group.[32] Anxious older adults in epidemiological and treatment-seeking samples retrospectively report an average duration of 20 years or more, at least in the case of GAD.[13,14,33,34]

Anxiety's association with disability is greater with increasing age and it is bidirectional.[35] Anxiety increases disability[36] and appears in some studies to be associated with increased mortality risk.[37-40] Additionally, significant quality of life impairment and increased burden of health care cost has been noted in GAD in older adults, on a par with that seen in late-life depression.[41,42]

Perhaps more uniquely in older adults, data suggest that chronic pathological anxiety is toxic to brain health. Anxiety symptoms or disorders in elderly are associated with accelerated cognitive decline.[43-45] Below are some putative mechanisms based on an examination of recent mechanistic research.

Chronic psychological distress in older adults results in impairments in cognition[46-49] and it is thought that a key mechanism for this relationship involves changes in the hypothalamic-pituitary-adrenal (HPA) axis.[50] The HPA axis is a neuroendocrine mediator of stress and its central nervous system (CNS) effects *(Figure 2)*.

The aging brain is less able to downregulate the HPA axis[51-56] and is more vulnerable to physiological insults.[57,58] As a result, in older adults, chronic anxiety can cause HPA axis hyperactivity,[59-64] with deleterious effects on memory and executive function.[48,53,61,65-75] The putative mechanism is an effect of high cortisol on brain structures (eg, hippocampus and prefrontal cortex) involved in neurocognition[76,77]: Chronically elevated cortisol desensitizes CNS glucocorticoid receptors,[78] altering glutamatergic N-methyl-D-aspartate receptor activity[79] with

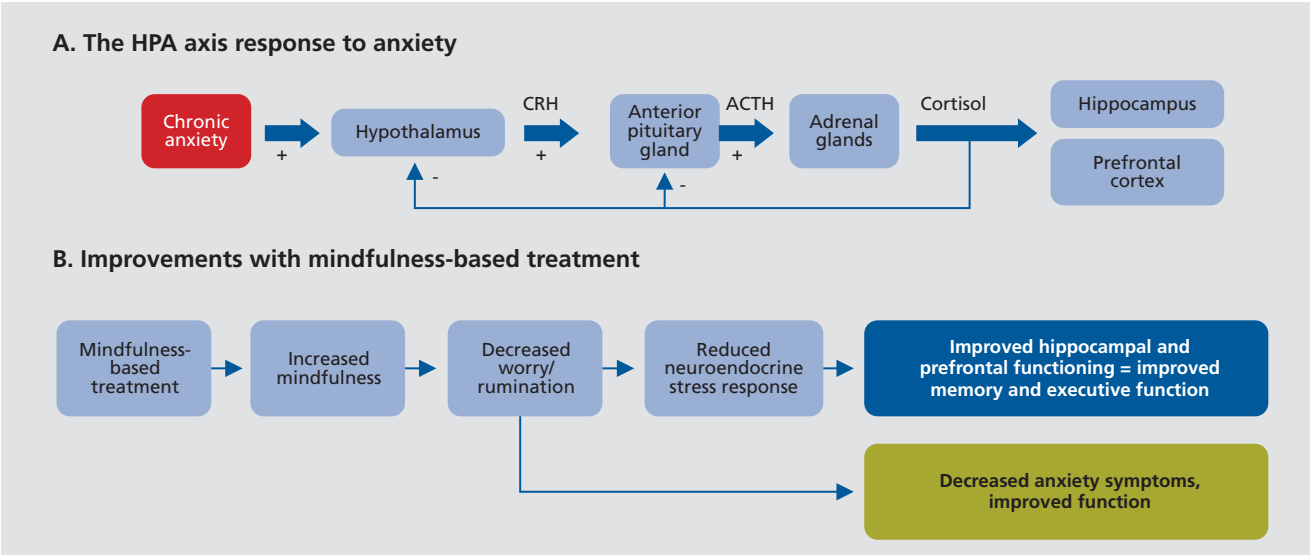


**Figure 2.** Proposed model of how a biological stress response in late-life anxiety produces cognitive impairment, and how mindfulness-based treatment for late-life anxiety disorders may reverse this cognitive impairment. CRH, corticotropin-releasing hormone; ACTH: adrenocorticotropin hormone

consequent synaptic and morphological changes in these structures.[69,80,81]

Some of these changes appear to be reversible.[69,82] For example, memory and hippocampal volumes in depression and anxiety disorders appear to be dynamic, increasing with successful treatment,[75,83,84] including in the elderly.[85] Thus, treatments for late-life mental disorders that reduce HPA axis hyperactivity ought to improve cognition. In a series of articles examining cortisol in late-life GAD, we found support for this hypothesis. We found that older adults with GAD had HPA axis hyperactivity, with 40% to 60% higher cortisol levels than comparisons.[61,86] We also found a neuroendocrine effect of treatment: subjects who received escitalopram had a 12% to 15% reduction in peak and total cortisol with escitalopram (vs no change with placebo).[86] The neuroendocrine effect was correlated with reduced anxiety. This indicated that HPA dysfunction in late-life anxiety is modifiable with treatment. Finally, we found that cortisol changes during treatment predicted memory improvement; that is, we found significant improvements in immediate and delayed memory in escitalopram-treated subjects whose cortisol levels decreased.[87] In all, this research suggests that reducing the biological stress response might be one treatment target for cognitive improvement in late-life anxiety disorders, which we discuss further later in this review.

A chronically elevated stress response seen in late-life anxiety may cause cognitive decline by other mechanisms. Some studies have found increases in β-amyloid-42 peptide (Aβ42) production and tau hyperphosphorylation attributable to excessive HPA activation (mediated via corticotropin releasing factor-1 [CRF1]), showing a link between chronic stress in aging, increased CRF production, and the putative pathogenic steps in Alzheimer's disease[88-90]; this provides other putative mechanisms for cognitive decline in the context of chronic anxiety, mediated by excessive or altered HPA axis activation. Late-life depression is associated with immune activation, so this relationship might also be true in late-life anxiety.[91,92,93] Cardiovascular disease is the main cause of premature mortality in mental illness,[94] and some research has elucidated mechanisms between anxiety in elderly and cardivascular disease—insulin resistance, endothelial reactivity, and altered autonomic function.[95] Research in chronic psychosocial stress and reduced telomere length[96,97] has given rise to the hypothesis that chronic affective disorders lead to telomere shrinking[98]; hence chronic anxiety may be accelerating aging at a cellular level. Finally, altering serotonin function in an aging model appears to affect stress responsitivity as well as longevity and age-related neurodegeneration.[99]

An apt summary of these myriad findings would be that stress research and aging research are intersecting: accelerated aging and stress hyperreactivity (as seen in anxiety disorders) are overlapping concepts. Thus, for late-life anxiety disorders, agents that affect aging pathways (such as rapamycin or calorie restriction mimetics) may be among the novel treatments that benefit health and cognition. Unfortunately, despite the wealth of research in the stress, immunology, and aging fields that could be applied to elucidate these connections, no longitudinal research, to our knowledge, has been done or is underway to elucidate the long-term consequences of chronic pathological anxiety in late life, their mechanisms, and/or novel treatments to reverse this "accelerated aging" process.

## Comorbidity of anxiety with depression in the elderly

Depressed individuals at all ages, including older adults, commonly have comorbid anxiety symptoms or disorders. Longitudinally, anxiety symptoms appear to lead to depressive symptoms, more likely than is the case vice versa.[100] Anxiety disorders could therefore be a risk factor for late-life depression as well as a predictor of persistence and relapse, as in young adults.[14,101,102-106] Some research disputes this assertion.[107] On the whole, though, studies support the conceptualization of anxious depression as a severe, treatment-relevant subtype of depression throughout the lifespan. It remains unknown whether anxious depression reflects diagnostic or dimensional phenotypic overlap, a common neurobiological, behavioral, and/or psychological underpinning, or some additional heterogeneity. Anxious depression might be particularly relevant in older adults, in whom it predicts more cognitive decline[44] and greater suicide risk[108] than nonanxious depression.

## Treatment

Pharmacological treatments for anxiety disorders do not always have the same benefits or risks across the lifespan. Additionally, in the case of psychotherapy, treatments typically need to be adapted for older adults.[30,109]

This section summarizes treatment literature in geriatric anxiety disorders, discusses new directions in treatment development for older adults, and then provides a set of management guidelines for clinicians.

**Psychotherapy**

Cognitive behavioral therapy (CBT) is the mainstay for anxiety disorder treatment. In younger adults, it is a treatment of choice, particularly when exposure-based, for most anxiety disorders (although it is by no means the only effective approach in these cases). It remains unclear whether CBT is superior to other psychotherapy approaches in late-life anxiety disorders; however, this is presently the dominant and most widely available formal psychotherapy for anxiety disorders. CBT might be particularly effective for anxiety disorders in cognitively intact, motivated older adults who are able to learn new skills in CBT and use them effectively.[110]

CBT for late-life anxiety typically involves psychoeducation, relaxation, cognitive therapy, problem-solving skills training, exposure and habituation to anxiogenic situations, and sleep hygiene when necessary for insomnia, similar to treatment in younger adults.[111] In older adults, the most effective ingredient of CBT may be relaxation training, which is fairly simple for providers.[112] With respect to long-term management of this chronic disorder, naturalistic follow-up studies of older GAD patients treated with CBT have demonstrated maintenance of gains for up to 1 year following discontinuation of treatment.[113]

There are some limitations to CBT for older adults with anxiety disorders. First, both a meta-analysis and a small direct randomized comparison of pharmacotherapy and psychotherapy found medications to be more effective than CBT in the acute phase of treatment.[114,115] Additionally, although CBT has been shown to be effective in the primary care setting,[116] the lack of CBT therapists with experience in late-life anxiety is a barrier to widespread implementation.

Adaptations for older adults include a slower pace with increased repetition, less abstract cognitive restructuring techniques and correspondingly more focus on behavioral change, more focus on health concerns, and engagement of the family in the treatment. In addition to in-session discussion and a written summary of material, it is useful to audiotape sessions for participants to increase the learning of new material. Another possible adaptation is the integration of religion into CBT, particularly in older adults who often have more of a spiritual view of their lives.[117]

Modular treatment reflects a novel approach in psychotherapy research in which the patient's presenting problems or symptoms are used to choose the specific components of treatment.[118,119] This patient-centered process appears to increase engagement and reduce attrition[120,121] and may be more cost-effective.

Some other psychotherapy treatment modalities are worth mentioning. First, bibliotherapy, or guided self-help, has long been a low-cost and widely available alternative (or addition) to a full-scale psychotherapy protocol.[122] Such self-help guides exist using CBT, Acceptance and Commitment Therapy, or mindfulness models; they can be used as a first step in, or complement to, formal psychotherapy (or pharmacotherapy) approaches. A recent study of late-life anxiety and depression prevention used a stepped-care approach, in which the first intervention was bibliotherapy, was effective at preventing anxiety and depressive episodes.[29] Many self-help workbooks exist for anxiety disorders, though none to our knowledge are focused on older adults. There is increasing indication that many patients are using the Internet as a guide for treatment, although it is unknown to what extent this is the case for older adults. As such, Internet-based self-help may be another increasingly-available, low-cost psychotherapy option that is little-studied in this age group. Organizations such as the Anxiety Disorders Association of America and the Geriatric Mental Health Foundation offer psychoeducational help for late-life anxiety disorders on-line.

**Novel treatment directions for psychotherapy in late-life anxiety disorders**

Worry and rumination are important driving forces in late-life mental disorders.[123-125] Poorer executive function, which is associated with aging, is associated with decreased ability to inhibit rumination and worry.[126-130] Recent studies demonstrate that putative neuroimaging markers for rumination[131,132] increase with aging.[25,133-136] Worry and rumination are associated with HPA axis hyperactivity in late-life mental disorders; for example, we found that excessive worry robustly predicted cortisol levels in late-life generalized anxiety disorder (GAD) patients,[61] and that reduction of worry predicted cortisol reduction during treatment.[86]

These data generate the hypothesis that interventions that reduce pathological worry and rumination will reduce HPA axis hyperactivity and thereby improve cognition as well as clinical symptoms in late-life anxiety disorders and depression. Unfortunately, standard treatments for these disorders in older adults are of modest efficacy for pathological worry and rumination.[116,137,138] Thus, new and effective psychosocial interventions are needed.[139]

Hyperactive stress response due to pathological worry and rumination may be an ideal target for mindfulness meditation. Mindfulness meditation emphasizes focused, nonjudgmental awareness of present moment experiences as an alternative to dwelling on the past (eg, ruminating)[140] or future (eg, worrying).[141] One mindfulness-based intervention, Mindfulness-Based Stress Reduction (MBSR) has been shown to improve anxiety[142-144] and other psychological outcomes in clinical trials. It is already practiced in every major city in the US and in over 250 clinics, hospitals, and HMOs in the US and abroad.[145] Mindfulness meditation programs have seen an explosion of interest and acceptability among older adults.[146-150] MBSR appears to increase mindfulness,[151] a state of present-centeredness that is the converse of worry about the future and rumination about the past.[152] Accordingly, several studies have demonstrated a rumination- and worry-reducing effect of MBSR.[140,153,154] Accordingly, multiple studies of MBSR have demonstrated potent cortisol-lowering effects, suggesting that increasing mindfulness reduces excessive HPA axis responses.[155,156] Thus, MBSR appears promising, conceptually and empirically, as a treatment for the factors that underlie neurocognitive impairment and clinical outcomes in late-life anxiety disorders, as shown in the model in *Figure 2b*.

**Pharmacotherapy**

Benzodiazepines are still commonly used for geriatric anxiety.[157] However, the risk:benefit ratio of these medications is poorer in older adults than in younger adults. In older adults, these medications are associated with falls,[158] disability,[159] and cognitive impairment and decline.[160] The risks occur at doses lower than the usual efficacious dose of these medications for anxiety disorders. Thus, these medications do not just have a tight therapeutic index, they have a reverse index (dose for harms lower than dose for benefits) with increasing aging. For this reason, they should be considered short-term adjuncts to treatment, with long-term use only as a last resort.

Two small RCTs[115,161] provided important feasibility data and preliminary evidence of the efficacy of selective serotonin reuptake inhibitors (SSRIs) in the acute treatment of older adults with anxiety disorders, predominantly GAD. As a result, one of us (EJL) led the first and, to our knowledge, only full-scale RCT of an SSRI for acute treatment of late-life anxiety disorders.[137] We randomized 177 older adults with GAD to the SSRI escitalopram, flexibly dosed at 10 to 20 mg daily, or placebo for 12 weeks. Escitalopram was shown to be efficacious, with greater cumulative response (69% vs 51%, $P$=0.03) and greater improvements in worry severity and role function. The effect size for most clinical outcome measures was in the low-medium range. A reasonable conclusion from this full-scale study, together with the pilot studies, is that SSRIs are efficacious but show the same disappointing effect sizes as in studies of young adults (or older adults with depression).[162]

There are caveats to this conclusion: first, a single relatively small full-scale study is unlikely to be adequate for clarifying the extent of benefits for any treatment (although, as mentioned previously, we are unaware of any current efforts for another); perhaps the effect size of SSRIs is higher, or lower, than we found in that study. Second, all of these studies suffer the limitations of the measures used in anxiety trials, such as the Hamilton Anxiety Scale[163] and Penn State Worry Questionnaire. Finally, clinical symptomatology is not the only important outcome of late-life anxiety disorder treatment. In fact, it may be the least important, as patients are typically more concerned about their quality of life and their systemic and (in particular) cognitive health, such as memory decline. In that study, we measured quality of life (which improved, albeit modestly, more with escitalopram than placebo) and also cognitive health, using neuropsychological testing as a proxy.[164] We found that improvement in late-life GAD was associated with significant improvements in a variety of cognitive measures; however, patients randomized to escitalopram showed greater improvement than those randomized to placebo in only one neuropsychological testing—a sorting task that is a proxy for some aspects of executive function. Thus, although, as noted previously, in some individuals (namely those with reduction in cortisol during treatment) there were some cognitive improvements,

in the aggregate the SSRI treatment was disappointing for its acute benefits for cognitive function and quality of life. The SSRIs may be too nonspecific and "broad-spectrum" to hope for significant cognitive benefits in late-life anxiety treatment.

There have been no prospective studies of serotonin norepinephrine reuptake inhibitors (SNRIs) specifically in late-life anxiety as there have in late-life depression. A retrospective examination of phase 3 venlafaxine XR data found the drug to be efficacious in adults aged 60+, with an effect size (drug-placebo difference) and side-effect profile similar to younger adults.[165] Similar findings have been reported with duloxetine.[166]

These studies in SSRIs and SNRIs have found similar side effects in elderly persons as in younger adults, but importantly they were not designed to determine the recently reported potential risks of SSRIs specific to the elderly population: gait impairment increasing risk for falls,[167] and bone loss.[168] Other risks that are greater in older adults are impaired clotting leading to non-GI and GI bleeding[169] and SIADH leading to hyponatremia.[170] Such reports suggest that the risk:benefit ratio for long-term SSRI/SNRI use is not the same as in younger adults. These concerns have yet to be addressed in a properly constructed longitudinal study (ie, a randomized controlled trial with an adequate safety evaluation).

In terms of non-SSRI/SNRI treatments, a large-scale study with pregabalin in geriatric GAD showed efficacy.[171] Pregabalin is not FDA-approved to treat anxiety disorders; its mechanism of action for anxiety is unknown—it binds to an auxiliary subunit voltage-gated calcium channels and is thought to reduce the synaptic release of several neurotransmitters. Mirtazapine is another non-SSRI/SNRI treatment with efficacy in anxiety, with some evidence specifically in late-life anxiety disorders.[172]

Most geriatric anxiety pharmacotherapy research has focused on GAD. There has been one promising study of the SSRI citalopram in older adults with PTSD,[173] and also evidence that the α-adrenergic antagonist prazosin is efficacious for sleep-related concerns in PTSD, although not for other PTSD symptoms.[174] There are two small studies in late-life panic disorder: Rampello et al[175] found superiority of escitalopram over citalopram in time to response, and a small open-label study found promising signals with sertraline.[176] Finally, in GAD in the context of stroke, one analysis found efficacy of nortriptyline in a merged dataset of several RCTs of post-stroke depression, in which patients with comorbid GAD were analyzed.[177]

The only published augmentation study in late-life anxiety disorders is a small study with risperidone.[178] While the atypical antipsychotic was promising, there have been concerns with atypicals in older adults, given evidence of higher mortality with antipsychotics in older patients with dementia, and metabolic effects including weight gain, elevated lipids, and insulin resistance. It is unclear whether the mortality risk applies to nondemented older adults, but the metabolic risks certainly do.

Finally, long-term or maintenance treatment of late-life anxiety with medication has not been studied (although we are currently carrying out a study of maintenance effects of SSRI treatment in late-life GAD), and no augmentation strategies can be recommended with confidence.

**Combining medication and psychotherapy for late-life anxiety disorders**

The inadequacy of monotherapy is well known in mood and anxiety disorders, and combination treatments may be more effective.[179] Antidepressants and CBT have different mechanisms and may be able to treat different components of the illness.[180,181] Combination treatment in older adults might best be carried out sequentially, rather than simultaneously initiated, to maximize cost-effectiveness and allow the patient and provider to focus sequentially on different aspects of treatment, rather than divide focus among multiple treatments and components of illness at once.[182] The hope is that, with two treatments targeting the different facets of the illness, persistent residual features and relapse are less likely.

Supporting this assertion, a recent review of meta-analyses concluded that psychotherapies involving cognitive and behavioral strategies for GAD are superior to nondirective therapy and pill placebo, and equivalent to pharmacotherapy in the acute phase of treatment, with robust effects extending as far as 10 years following discontinuation of treatment.[183] In one study of anxious older adults, benefits of CBT were increased at 1-year follow-up in patients who had been treated for at least 3 months with medications prior to receiving CBT, suggesting that sustained or increasing gains are possible for older adults receiving CBT for anxiety following an acute course of pharmacotherapy.[184]

The strategy of sequencing medication with CBT is con-

troversial in the anxiety disorders.[185,186] Pharmacotherapy might interfere with the challenging of catastrophic beliefs during psychotherapy, individuals treated with medications may be less motivated to engage in psychotherapy, and psychotherapy in the context of medications may result in state-dependent learning that does not persist after the medication is discontinued.[187,188] Because of this, we are currently testing the strategy of sequenced medication and CBT within a controlled study design.

**Future directions in treatment development: new targets and one large barrier**

The preceding sections raise several avenues for novel treatment development. Our findings with cortisol in late-life GAD are summed up as such: elevated cortisol is associated with GAD, is reducible with treatment, and when reduced during treatment is associated with neuropsychological improvements (in memory). Thus, the biological stress response (for which cortisol is a mediator or proxy) may be a prime target for novel pharmacological (ie, cortisol-blocking) or behavioral (ie, worry-reducing) strategies, with the effect of improving not only clinical but also cognitive functioning. Conversely, researchers also need to consider how to improve anxiety in cognitively-impaired older adults, particularly those whose impairment has evolved into dementia, realizing that for many if not most, such a level of cognitive impairment is not likely to improve with any treatment (anxiety or otherwise).

The biological stress response may also be a target in improving systemic health in late-life anxiety disorders. The dramatic health impact not only of late-life anxiety disorders but also in other chronic stress models, such as is seen in spousal caregivers of AD patients, suggests that more mechanistic work is needed to delineate the pathways from psychosocial stress as seen in chronic anxiety/worry to adverse health. Fortunately, new tools (such as genome-wide expression or proteomic analysis, or novel imaging techniques to measure CNS or peripheral inflammation) should make this research more feasible. Less mechanistic than a specific biological pathway but at least as important is the concept of function as a target. Anxiety disorders are disabling, just as is depression in older adults. For example, fear of falling is in some patients a highly disabling condition akin to severe agoraphobia. New methods are needed to measure and improve function in older adults that is relevant to anxiety disorders.

In terms of one major barrier to progress in late-life anxiety research, we turn again to the issue of measurement. Progress in measurement techniques is a prerequisite for scientific advances, yet in the area of late-life anxiety disorders our measurements are antiquated and demonstrably inadequate, hampering research progress. This is true across the lifespan but may be particularly pressing in geriatrics. We have previously reviewed this issue of inadequate measurement in some depth[30] but will summarize key concerns here.

Variability in diagnostic criteria and tools leads to discrepant epidemiological findings: as reviewed in-depth elsewhere,[2] epidemiologic studies have found dramatically different prevalence and incidence estimates. Numerous issues hamper our ability to accurately diagnose or characterize anxiety disorders in older adults,[189] and a recent review has suggested ways to improve diagnosis so that *DSM-5* might be more sensitive to late-life anxiety disorders.[4] Additionally, it has been suggested that the problems described above reflect the limitation of using diagnostic categories, and the solution is to move towards dimensional assessments of illness.[190] Yet, the challenge of measuring geriatric anxiety goes beyond diagnosis. The problems of symptom assessment in geriatric mental health are complex and not necessarily ones that can be resolved with existing or adapted symptomatic assessments. Instead, technological advances could develop novel ways of monitoring the severity and phenomenology of anxiety and its response to treatment. These advances include: (i) improved subjective symptom measurement via electronic daily or momentary assessment; (ii) improved measurement of function via actigraphy and other assessments; and (iii) assessment of the physiological and cognitive benefits of treatment via biomarkers. These are described in more detail below.

*Electronic assessment of symptoms*

Anxiety symptomatology has traditionally been assessed using retrospective self-report.[191-197] Such measures require participants to recall, average, and summarize their experiences and are subject to bias and error; for example, disproportionate weight may be given to highly significant past instances relative to current or ongoing events.[198-207] Current state assessment seems critical for

anxiety, often a moment-to-moment waxing and waning experience.

Ecological momentary assessment (EMA) involves repeated measurement of momentary experiences naturalistically and in real time.[208] It has been used to assess stress, behavior, and other physical and mental health-related constructs.[209-214] The key features of EMA are that it samples: (i) present moment experience (ie, as opposed to recalled, averaged, or summarized experience); (ii) in its natural context (ie, outside of a laboratory); (iii) repeatedly over time (often up to eight times per day). The availability of electronic means of data capture, such as mobile devices, has greatly facilitated the use of EMA. For example, participants can be prompted at random intervals by a device to respond to a brief series of questions about the present moment; responses are input immediately by the participants, with data transmitted wirelessly to the investigator.[215-217]

Given its capability of evaluating momentary experience, EMA appears well suited to examine anxiety symptomatology. EMA avoids reporting biases such as recency and severity effects, "telescoping," and difficulties with estimation. These biases are particularly relevant for elderly. These types of assessments can also capture diurnal variations in symptoms. Yet even these assessments require a fair degree of insight by the user; we may need assessments of anxiety severity that do not require subjective assessment by the patient.

*Novel measures*

Novel measures may also improve our measurement of disability (or behavior change) stemming from anxiety. Actigraphy findings have been used to measure depression severity and treatment response.[218-220] Actigraphy is particularly useful in examining sleep, activity, and circadian rhythm, so these patterns could potentially provide an objective measure of response that could complement self-report. A similar use of objective assessment technology might be the use of global positioning (GPS/GIS) to gather extensive data on activity and therefore on function.

*Biomarkers*

Finally, measurement of biomarkers may be able to characterize one aspect of anxiety disorders most notable in older adults: their deleterious effects on cognitive and physiological health. Neuropsychological testing has long existed (though rarely examined in treatments of anxiety disorders). Newer biomarkers could evaluate treatment response in older adults in whom anxiety is most likely to have long-term adverse health or cognitive consequences. These may include HPA axis functioning through cortisol sampling, or genome-wide expression analysis, a powerful high-throughput technology that provides a systems approach for examining complex clinical disease in terms of dynamic changes in gene expression.[221] Genome-wide expression analysis assays the current activity level of all transcripts known in humans. Thus, for example, a researcher can determine whether stress results in higher or lower levels of RNA transcripts in peripheral immunological cells.[222] Such data, combined with bioinformatic techniques, allow researchers to infer the functioning of all of the intracellular pathways at a given point in time (ie, at baseline and then after a treatment), as well as their interactions.[223,224] Additionally, as we previously noted, chronic stress hyperactivity (as seen in anxiety disorders) may cause accelerated aging; thus, telomere length measurement, during the course of a treatment study, might provide a precise and quantitative estimate of benefits of treatment for health and cognition of older adults. Finally, novel neuroimaging markers might include neurogenesis, functional connectivity, and peripheral and central inflammation. In all, recent advances in technology in studies of anxiety could increase our precision for measurement, a need most pressing in geriatrics.

## What we do know: eight rules for managing anxiety disorders from a lifespan perspective

In this last section, we provide a blueprint for managing older (and equally so, younger) adults with anxiety disorders, based on empirical findings and our own clinical experience.

**1. Assessment should measure severity and provide objective criteria for assessing response, and should assess comorbidity, prior treatment, cognitive status, and need for a medical workup**

Assessment of anxiety is often overlooked by mental health providers. A helpful introduction to the topic is to ask about stress; eg, "older adults often deal with stress;

how do you feel in times of stress?" Patients who describe symptoms suggestive of anxiety or worry can then be further queried. Use nondirective questioning to determine the severity of anxiety symptoms, by: (i) level of distress (asking how much the anxiety symptoms bother the patient, what strategies they are trying in order to control or avoid it, and what somatic symptoms they are having); (ii) how much of their time it takes; and (iii) avoidance. Avoidance is a key component of all anxiety disorders yet often is not recognized. For example, older adults may rationalize changes in behavior patterns to perceived poor health or environmental limitations. Inquire about behavioral changes including activities given up or, conversely, intrusive overinvolvement with family members. Talk to the family for corroboration.

We are often asked about differentiating anxiety from depression. In our experience, some patients (and some neurobiologists!) fail to appreciate the importance we place on this diagnostic distinction. Clinically, the clinician will often have to deal with anxiety as well as depression in a patient.

The medical differentiation of late-onset anxiety is long but should chiefly consider: (i) depression; (ii) cognitive impairment (dementia, delirium); (iii) anxiety-inducing medications (or recent discontinuation or inconsistent use of sedatives); and (iv) common and rare medical conditions that could masquerade as an anxiety disorder. Regarding the latter, consider thyroid disease, B12 deficiency, hypoxia, ischemia, or metabolic changes (eg, hypercalcemia or hypoglycemia).

**2. Think twice about a benzodiazepine prescription**

As previously noted, benzodiazepines, like any sedatives, have a poorer risk:benefit ratio in elderly persons than in young adults. Therefore, long-term use of benzodiazepines appears unfavorable in this age group. Patients should be warned about the potential risks associated with these medications.

Benzodiazepines provide a fast anxiolytic action, so a common recommendation is to use these medications at low dose as a short-term adjunct, in which case they may provide some early relief and improve adherence to the treatment regimen. Even this adjunctive use of benzodiazepines is typically unnecessary and can reinforce an inappropriate message to patients that anxiety must be immediately relieved, which is akin to an avoidance response.

**3. Psychoeducation about anxiety and treatment, including potential health benefits**

Psychoeducation may be the most important management step. Providers should inform patients that they have a treatable condition and should address stigma, misinformation, and other common and surmountable barriers to treatment. Emphasize the importance of treating anxiety for improving quality of life, health, and brain health. Include the family in these discussions.

**4. First-line treatment according to patient's preference, provider preference and competence, and treatment availability**

First-line options include one or more of the following: SSRI, SNRI, relaxation training, and CBT. Bibliotherapy can and should be recommended alongside any of these options. Often these options will need to be started along with, or after, discontinuation of harmful or inappropriate confusogenic medications such as sedatives, anticholinergics, and antihistaminergics.

| | Childhood/adolescence | Adulthood | Old age |
|---|---|---|---|
| Key presenting complaints | Irritability, poor sleep, somatic symptoms | Fatigue, poor sleep, irritability, somatic symptoms | Poor concentration or memory, fatigue, poor sleep, somatic symptoms |
| Contexts | School | Work, social settings | Activities of daily living, health care settings |
| Burden | School refusal, burden on parents | Occupational disability, interpersonal dysfunction, excess health care utilization | Excess health care utilization, caregiver burden, cognitive decline, cardiovascular and other age-related disease, excess disability, premature mortality |
| Main comorbidities | Depression | Depression, substance abuse | Depression, dementia |

**Table II.** Features of anxiety disorders across the lifespan.

**5. Frequent follow-up, particularly within the first month of treatment or dose change, to encourage adherence and monitor treatment response**

Most anxious adults will receive a pharmacological trial as first-line treatment. Older adults vary from young adults in terms of increased comorbid medical conditions, pharmacokinetic changes, frailty, and drug interactions. Yet, anxious older adults' reports that they are sensitive or intolerant of antidepressant medications appears to result less from actual side effects than from their anticipatory concern, vigilance towards interoceptive stimuli, and tendency to catastrophize about any interoceptive sensations they detect.

Overcoming such fears related to the medication's potentially negative effects is not an easy task. This task is made more difficult by the standard list of potential side effects with any medication, many of which sound frightening or are symptoms that the patient already has (eg, fatigue, insomnia). To combat these fears proactively, describe how such antidepressant medications have established efficacy and high tolerability. Also, a health care provider should describe their experience in prescribing this medication and state that, while side effects are possible, no particular side effect is inevitable: most patients taking the medication will either have no side effects or will have brief, self-limited side effects which subside in a few weeks. Emphasize that the medication is unlikely to be incapacitating. When patients mention that "I already have that symptom," they are not more likely to have that as a side effect as a result; in contrast, physical symptoms tend to decrease with pharmacological treatment.[225]

Family involvement can help with adherence. Nevertheless, most patients will have additional concerns after the medication is prescribed, especially before and just after they take the first dose. Address this in several ways, stating to patients/families that it is natural to have questions, and encouraging them to call, providing 24-hour contact information (typically patients do not, but benefit from the knowledge that they can). Ideally, as in clinical trials, we would provide weekly visits, or bi-weekly visits with interim telephone contacts, for the first month of treatment and the month subsequent to a dose increase, since this is when patients are most likely to develop concerns about side effects.

Follow-up includes interviewing patients closely for any concerns about perceived side effects. Patients often seem to perceive as side effects symptoms that predate the start of medication and are clearly a component of the disorder. In anxiety, adherence issues stem from vigilance to perceived side effects and subsequent catastrophizing. If such an issue is noted, an immediate contact will reassure the patient that they are being monitored closely by experts and that the medication is not causing some sort of severe or worsening problem. This brief but timely intervention reduces premature discontinuation of pharmacotherapy.

Geriatric anxiety disorder patients usually get better, but given the fluctuating nature of the disorders and the issues with insight, they often do not realize they are improving. Repeated assessment of frequency and severity of anxiety is important not just for assessing success of treatment but also demonstrating improvement to the patient.

**6. With medications, start low, go slow, but go—as aggressively as required to treat symptoms to remission**

After psychoeducation and clean-up of inappropriate medications, the proximal goal of acute care is to get the patient a treatment trial of sufficient intensity and dura-

| |
|---|
| **Diagnostic** |
| -Older adults appear to have lower overall prevalence of anxiety disorders, compared with younger adults. |
| -It remains unclear whether these lower rates reflect a true decline in anxiety, changes in presentation of anxiety, or difficulties with detecting and diagnosing anxiety disorders, with aging. |
| -Anxiety disorders remain common, chronic, and highly impairing disorders in old age. |
| **Presentation** |
| -A presentation of worry predominates more so than panic or phobias in old age, which is a reversal of earlier in the lifespan. |
| -The key impairments of anxiety disorders vary across the lifespan (chiefly school in young age, work in adulthood, and health care utilization and caregiver burden in old age). |
| **Treatment** |
| -Sedative anxiolytics, including benzodiazepines and antihistamines, have a poorer risk:benefit ratio in older adults. |
| -Other pharmacological strategies appear equally effective (or ineffective) in older and younger adults. |
| -Psychotherapy appears less effective in older adults than younger adults, possibly due to cognitive impairment imposed by the anxiety disorder in this age group. |

**Table III.** Key points from a lifespan view of anxiety disorders.

tion to improve symptoms. This requires dose optimization, often at high doses that do not vary across the lifespan in the case of SSRIs/SNRIs.

**7. Consider augmentation treatment and refer to experts if necessary**

Monotherapy is usually inadequate, and if a good trial is only partially effective, add another. Providers should not "run out of options" but then should refer a patient to someone with additional expertise in (eg, a geriatric psychiatrist or a psychotherapist skilled at treating anxiety disorders).

**8. Provide maintenance treatment; evaluate the need for such if treatment is discontinued**

Since anxiety is chronic, treatment will usually need to be long-term, ie, maintenance medication and/or booster psychotherapy sessions. As the patient has already overcome any fears or initial side effects, maintenance pharmacotherapy requires less frequent oversight though continued monitoring of clinical changes, side effects, and changes in coprescribed medications is necessary.
If a patient chooses to taper off a medication, they should be informed that they may need to resume treatment in the event of relapse. A taper should be very gradual (ie, over several weeks) to avoid rebound anxiety symptoms. Management does not have an end point, even when the patient is no longer receiving active pharmacotherapy. In the case of psychotherapy benefits, booster sessions provide important reminders to continue to use effective new coping skills.

## Summary

Anxiety disorders are neurodevelopmental disorders, and as neurodevelopment continues and changes throughout the lifespan, even into old age, there are new, unique issues with anxiety disorder and presentation at each point in aging. Just as childhood offers unique perspectives such as the need to target parental influence[226] and the possibility for prevention, in older adults there are new presentations (such as FOF) and new effects of anxiety (on brain and physiological health).
There have been many strides in our understanding of anxiety disorders across the lifespan, but also many gaps in our knowledge remain. The field has adequately clarified the benefits of treatments developed for young adults, as equally efficacious in older adults in the case of pharmacotherapy, or in the case of cognitive-behavioral therapy, needing adaptation in order to be efficacious. What is lacking are new treatments for older adults and the understanding of the mechanisms for onset and maintenance of anxiety disorders and how they exert such deleterious effects on the brain and physiologic health of older adults.
New treatments, both behavioral and somatic, need to be developed and tested across the lifespan. In older adults, treatment development ought to consider the barriers posed by cognitive impairment and even develop treatments that target cognition as well as clinical symptoms. Research needs to consider and address the gaps raised in this review, most fundamentally our limitations in the diagnosis and measurement of anxiety disorders in older adults. The great public health importance of this research is highlighted by the graying of the world population, the high human and economic cost of anxiety disorders in all age groups, and the potential for existing and new treatments to reduce much of this burden. ❑

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### *Una visión de los trastornos ansiosos a lo largo de la vida*

*Los cambios en el neurodesarrollo durante el curso de la vida, desde la niñez pasando por la adultez y hasta la vejez, tienen importantes repercusiones para la instalación, presentación, curso y tratamiento de los trastornos ansiosos. Este artículo presenta datos acerca de los trastornos ansiosos en la forma cómo ellos aparecen en los adultos mayores en comparación con los más jóvenes. Este artículo se centra en los cambios relacionados con la edad en la epidemiología, presentación y tratamiento de los trastornos ansiosos. Además, este articulo describe algunas de las brechas y limitaciones en nuestra comprensión del trastorno ansioso y sugiere directrices de la investigación que puedan aclarar los mecanismos de aquellos cuadros que se desarrollan más tardíamente en la vida. Finalmente se describe el manejo óptimo para los clínicos de los trastornos ansiosos a lo largo de la vida en "ocho pasos simples".*

### *Une perspective sur la vie entière des troubles anxieux*

*Les modifications neurodéveloppementales survenant tout au long de la vie, de l'enfance à l'âge adulte jusqu'à la vieillesse, ont des implications importantes sur la survenue, le cours et le traitement des troubles anxieux. Cet article présente des données sur les troubles anxieux tels qu'ils apparaissent chez les adultes plus âgés, comparés à ceux moins avancés en âge. Nous nous intéressons ici aux modifications liées au vieillissement dans l'épidémiologie, la présentation et le traitement des troubles anxieux. Cet article décrit aussi les lacunes et les limites de notre compréhension et suggère des directions de recherche pouvant élucider les mécanismes du développement du trouble anxieux plus tard dans la vie. Enfin, nous décrivons la prise en charge optimale des troubles anxieux au cours de la vie, en « huit étapes simples » pour le médecin.*



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