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Anxiety disorders: new developments in old age

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We are pleased to provide a guest editorial to this 5th special issue on geriatric anxiety in the American Journal of Geriatric Psychiatry (previous issues: January 2005, August 2007, October 2008, June 2009). Until about 10 years ago, geriatric anxiety disorders largely escaped clinicians' and researchers' attention for a variety of reasons that were specified in the first AJGP special issue in anxiety disorders [1] ; namely, anxiety disorders do not commonly present in geriatric psychiatry settings unless comorbid with depression or dementia, the disorders are difficult to detect and diagnose in this age group, many anxiety disorders (such as social phobia) typically present early in life, and many if not most anxious elders are reluctant to participate in treatment. Despite these obstacles to detection, diagnosis, and treatment, significant progress has been made in understanding the course, prognosis, and treatment of anxiety disorders in elderly. *It is reasonable to ask now: what do we know, and what do we still need to know?*

What we know

Anxiety disorders, once thought to be rare or even nonexistent in older adults, are now known to be common in this population. The disorders impair function and quality of life and may increase risk for other serious medical problems such as depression, dementia, and heart disease. Finally, just as geriatric mental health researchers in late-life depression have ably characterized the efficacy of established pharmacological and psychotherapeutic treatments, a much smaller literature in late-life anxiety has examined the efficacy of SSRI[2] and dual reuptake[3] antidepressants and cognitive-behavioral therapy (CBT).[4] In summary, we know that anxiety disorders are common, severe, and treatable in seniors, with potential benefits for reducing risk of many of the major age-related illnesses.

Yet there remains a treatment gap in the community: anxiety disorders in older adults are rarely detected and essentially never correctly diagnosed. As a result, the de facto treatment algorithm for an older adult in the community is: (1) nothing; (2) benzodiazepines, sedatives, muscle relaxants, and other management of somatic manifestations (e.g., referral to specialty medical clinics such as gastroenterology or cardiology for extensive diagnostic tests and potentially inappropriate treatment), which often makes matters worse than doing nothing; and (3) antidepressant monotherapy. The use of evidence-based psychotherapy,

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combined treatments, or collaborative care for anxiety disorders is unheard-of in this age group. It is thus worth discussing the articles in this special issue in the context what we still do not know.

How common are anxiety disorders in older adults?

The answer to this question depends on the study. Two papers in this issue exemplify the concerns regarding late-life anxiety epidemiology. First is the paper by Mackenzie and colleagues which finds a 2.8% prevalence of GAD in the large NESARC study, which included over 12,000 adults aged 55 and older.[5] They note this is a lower estimate than in younger adults, but also they note that the variance of GAD prevalence estimates in epidemiological studies is much greater in older than younger adults, with a range from 0.7% to 9%. Such 10+ fold prevalence estimates are typical for all of the late-life anxiety disorders. These wide estimates raise the question of just how appropriate diagnostic measures of anxiety are for this age group.

Similarly, the article by Grenier et al, in a large epidemiologic study of older adults in Quebec, finds that the combined prevalence of syndromal plus subthreshold anxiety (including those with symptoms of anxiety not meeting criteria for a disorder) is 26.2%.[6] Moreover, those with subthreshhold anxiety appeared similar to those with syndromal anxiety disorders in terms of comorbidity and use of health services or benzodiazepines for anxiety. Their conclusion is that diagnostic threshold criteria do not seem to discriminate between those with or without a severe condition needing mental health services. Readers of this journal will recognize parallels with subsyndromal depression, as articulated in a previous editorial by Martha Bruce, Ph.D. [7]: what do we do with those folks? That is, how do we delineate those older adults who have a mental health problem that would benefit from treatment from those who don't? It seems that given the heterogeneous nature of these “subsyndromal” problems, further study of the nature of anxiety as well as depressive presentations in late life would be most useful.

We conclude that there is no good answer to the question of “how common” or even “what” are anxiety disorders in the elderly. We recently served on a DSM-V workgroup on late-life anxiety disorders, which recommended that anxiety researchers involved with DSM-V should consider aging-related diagnostic and measurement concerns so that diagnoses, and diagnostic tools, are adequately sensitive to older adults. Additionally, there has been too little neurobiological research in late-life anxiety, with only one NIMH grant ever funded (a career development award that commenced in 2010) in this important area.

How do anxiety disorders negatively impact the health of older adults?

Numerous reports suggest that chronic anxiety is deleterious to the physiological and cognitive health of older adults, potentially leading to cancer, cardiovascular disease, and dementia. While some of this relationship may be due to unmeasured morbidity or reverse causality (e.g., pre-clinical Alzheimer's disease leading to anxiety complaints), of most interest to the geriatric mental health field is the proposition that chronic, uncontrolled stress (as seen in GAD and other anxiety disorders, as well as in depression) may set off a biological cascade that potentially increases the risk for a host of aging-related diseases.

Supporting this line of inquiry, Wilson and colleagues examined a large, longitudinal dataset of older adults who completed self-report measures of neuroticism and were then followed to a diagnosis of dementia.[8] They find that higher levels of anxiety and vulnerability to stress, but not other facets of neuroticism such as depression or self-consciousness, predicted increased risk of Alzheimer's disease and more rapid decline in global cognition. These results add to the growing literature tying anxiety symptoms and disorders in late-life with cognitive impairment and dementia [9].

Isingrini and colleagues used a mouse model of chronic uncontrolled mild stress (a mouse model of depression that is likely equally applicable for stress-related anxiety disorders such as GAD) to examine long-term, late-onset changes in markers of vascular risk.[10] They show late-onset increases in these vascular markers which are not prevented by treatment with fluoxetine. These results mirror findings in epidemiological studies of a relationship between anxiety symptoms and disorders with the subsequent onset of vascular disease, including coronary artery disease[11, 12] and begin to suggest one mechanism of this relationship, wherein chronic stress evoked in the anxiety disorder leads to molecular changes in vascular function.

Much remains unknown regarding the mechanisms from anxiety to cognitive and physiological health declines: Is it the result of an exaggerated biological stress response? Amyloid processing and deposition changes? Sympathetic nervous system changes? Inflammation? As we get better, more sensitive and specific (mechanistic) biomarkers, both in brain and systemically,[13] longitudinal research may be able to elucidate these mechanisms, thus linking late-life anxiety research to translational research in aging and leading to new treatments that mitigate or delay cognitive and physiological decline in aging.

And speaking of new treatments…

There is concern that the NIMH leadership's call for focusing on new treatments undercuts geriatric mental health intervention research, the goal of which is often to clarify the risk/benefit ratio (often qualitatively different in older adults) of existing treatments and/or adapt these treatments for this age group. Additionally, the dissolution of the NIMH intervention study section that included experts in aging (ITSP) and its incorporation into the general study section for adult mood and anxiety disorders interventions (ITVA) means that a geriatric anxiety grant will be reviewed mostly by individuals with expertise (and therefore scientific enthusiasm) in neither geriatrics nor anxiety disorders.

These two recent changes in the intervention research funding landscape pose great challenges for treatment research in late-life anxiety disorders. Nevertheless, we need to develop and personalize novel pharmacological and psychological therapies (and their combinations) for late-life anxiety disorders. Bradford and colleagues' study is a helpful step in this direction by asking who might not be well-served by standard treatment.[14] In a sample of 76 older GAD patients who received either 12 weeks of CBT or enhanced usual care, they found that individuals who had early response, as defined by a reduction in self-reported worry severity and controllability after four weeks, also had better long-term

outcomes as long as 15 months. The ability to predict long-term treatment response after only four weeks of treatment could be of enormous value in determining how to personalize treatment, including providing augmentation or an alternate treatment to those who are unlikely to get well and stay well on standard monotherapy. Two current studies with older GAD patients are examining this issue: Dr. Laszlo Papp and his colleagues at Columbia are investigating whether those who do not respond to four weeks of CBT will do better with the addition of pharmacotherapy, and we are investigating whether adding CBT after a 12 week course of SSRI medication will enhance response and/or prevent relapse after treatment discontinuation.[15]

In terms of medications for late-life anxiety disorders, no clear-cut predictors of response exist, although recent data suggest that genetic variability at the serotonin transporter may predict variability of antidepressant treatment outcome.[16] Missing from this special issue (and indeed the entire late-life anxiety field) are novel treatments as a true alternative (or augmentation) to antidepressants and CBT. It is hoped that the NIMH's mandate for novel treatment development will spur research in this area, as has been recently generated for late-life depression [17, 18].

Finally, no treatment, no matter how efficacious, is worthwhile if it does not actually get used, and used optimally. Late-life anxiety treatment effectiveness and dissemination research is practically non-existent; it is no surprise, then, that the vast majority of cases go undetected and un- (or under-, or mis-) treated. A few promising leads include relaxation,[19] mindfulness training,[20] bibliotherapy [21], and stepped care prevention [22], all of which are cost-effective.

The Dutch stepped-care study is noteworthy because it found that treatment that prevents the onset of late-life depression appears also to prevent late-life anxiety disorders. A great deal of evidence suggests that depression and anxiety are in fact a unitary disorder; for example, scores on depression and anxiety symptom scales are highly correlated[23]; both conditions respond to SSRI medications; some, although not all, anxiety disorders share a genetic diathesis with depression; and so on. In fact, the strongest evidence for a distinction between these conditions may come from research with older adults: behavioral/psychotherapeutic treatments for geriatric anxiety appear to work much less well than these treatments do for geriatric depression[24]. The same is not true for younger adults or for pharmacotherapy, which works equally well for anxiety and depression in elderly individuals. Therefore, from the perspective of a psychotherapist, determining whether an older patient has depression or anxiety is important in order to predict the likelihood of treatment response and/or the advisability of referral for a different form of treatment. Uncovering the cause of this discrepancy would not only have substantial clinical impact (especially since many anxious older individuals are anxious about the effects of medications and would prefer an effective nonpharmacological treatment) but potentially important scientific implications with respect to the etiology of mood and anxiety disorders.

In summary, the articles in this issue represent interesting advances in the field of geriatric anxiety research. Ultimately, we hope that such research will lead to better detection and

treatment of anxiety in older adults, with a resulting substantial impact on global health. The AJGP is wise to continue to highlight new developments in this important topic.

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