Curr Treat Options Psych (2017) 4:33–46
DOI 10.1007/s40501-017-0102-4

Geriatric Disorders (D Steffens and K Zdanys, Section Editors)

Pharmacological Management of Anxiety Disorders in the Elderly

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Published online: 10 February 2017

This article is part of the Topical Collection on *Geriatric Disorders*

Keywords Anxiety · Anxiety disorders · Elderly · Older adults · Selective serotonin reuptake inhibitors · Serotonin and norepinephrine reuptake inhibitors

Opinion statement

Anxiety disorders are common in the elderly. Additionally, anxiety symptoms often accompany comorbid psychiatric, medical, as well as neurodegenerative diseases in the older population. Anxiety in the elderly, often accompanied by depression, can lead to worsening physical, cognitive, and functional impairments in this vulnerable population. Antidepressants are considered first-line treatment. Both selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are efficacious and well-tolerated in the elderly. Some SSRIs are strong inhibitors of the cytochrome P450 hepatic pathway whereas others have less potential for drug interaction. Those antidepressants with more favorable pharmacokinetic profiles should be considered first-line in the treatment of anxiety. Mirtazapine and vortioxetine are also considered safe treatment options. Buspirone may have a benefit, but lacks studies in elderly populations. Although tricyclic/tetracyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) may be effective in the elderly, their side effect and safety profiles are suboptimal and thus are not recommended in late-life. Benzodiazepines and beta-blockers should generally be avoided when treating anxiety in the elderly. There is not enough evidence to support the use of antipsychotics or mood stabilizers given their risk of problems in both the long- and short-term. In addition, antipsychotics have a black box warning for increased mortality in elderly patients with dementia.

Introduction

According to the Population Reference Bureau, the number of Americans ages 65 and older is projected to more than double from 46 million today to over 98 million by 2060. Additionally, the 65-and-older age group's share of the total population will rise to nearly 24 from 15% [1]. Anxiety disorders are among the most prevalent mental health issues in the elderly [2]. A systematic literature review revealed that the prevalence of anxiety disorders in clinical settings ranges from 1.2 to 28% in elderly patients [3]. Additionally, a population-based study found that 18% of elderly patients receiving contracted home care in the USA have some type of anxiety disorder [4]. The most common anxiety disorders seen in older adults include generalized anxiety disorder and simple phobia [3, 5, 6]. It is important to note, however, that anxiety symptoms in the elderly that do not meet full DSM–V criteria can still lead to significant impairment and disability, requiring intervention.

Anxiety disorders in the elderly appear to be more likely associated with common medical conditions than those found in the general population [7]. Comorbid anxiety can complicate a patient's medical treatment and outcome. For example, the incidence of anxiety disorders in chronic obstructive pulmonary disease (COPD) patients is exceedingly common and ranges between 13 and 46%. Anxiety in these individuals is associated with functional limitations, poorer exercise tolerance, suicidal ideation, and higher frequency of hospitalizations [8, 9]. Anxiety and depression are also highly prevalent in patients with diabetes. A cross-sectional study of anxiety and depression in type 2 diabetes patients estimated prevalence to be 56.1 and 43.6%, respectively. The combination of depressive symptoms and anxiety symptoms in these patients was associated with poor glycemic control [10].

It is well-established that depression with co-occurring anxiety has been associated with an increased risk of cardiovascular and cerebrovascular morbidity and mortality [11, 12]. A recent systematic review concluded that the incidence rate for anxiety disorders after cardiac arrest varies from 13 to 42% [13]. Anxiety symptoms also frequently accompany patients with neurodegenerative diseases such as Alzheimer's and Parkinson's disease [14, 15]. Elderly patients with cognitive disorders often have faster cognitive and functional loss when accompanied by behavioral problems that may present with anxiety symptoms. Anxiety symptoms should be assessed in the context of medical or cognitive impairments in order to provide the right treatment and improve older individuals' over all well-being and outcome.

The pharmacological treatment of anxiety disorders in the elderly is complex at several levels. Multiple medical comorbidities can lead to worsening of psychiatric symptoms, and the use of psychiatric medications can potentially cause side effects, intolerability, and drug-drug interactions. Pharmacologic evidence for the treatment of anxiety in the elderly is limited. As such, clinicians must formulate an individualized approach to treatment, combining available guidelines from geriatric medicine and anxiety treatment for a younger-adult population. This paper reviews available evidence of pharmacological approaches to treatment of anxiety in the elderly.

Antidepressants

Antidepressants are the first-line treatment in anxiety disorders [16]. The selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are more commonly used in the elderly, due to their tolerability and safety profile in this population [17]. Although tricyclic/tetracyclic (TCA) antidepressants and monoamine oxidase inhibitors

(MAOIs) are indicated for select anxiety disorders, they are not considered first-line treatment of anxiety disorders in elderly patients due to side effects and safety considerations.

Serotonin-specific reuptake inhibitors (SSRIs)

Escitalopram is FDA-approved for the treatment of generalized anxiety disorder (GAD) and has demonstrated improvement in anxiety symptoms when compared with placebo in older adults [18, 19]. Additionally, escitalopram prevents symptom relapse. When augmented with cognitive behavioral therapy (CBT), it decreases the need for long-term pharmacotherapy use [20••]. In a recent study that included elderly subjects with social anxiety, the efficacy and tolerability of escitalopram versus placebo was compared. The primary efficacy analysis showed no difference for escitalopram 10 mg versus placebo. However, there was a statistically significant difference when escitalopram 20 mg was compared to placebo. The most common side effects were somnolence, nausea, and ejaculation disorders similar to younger subjects [21]. Escitalopram and citalopram also demonstrated benefit for treatment of elderly individuals with panic disorder [22].

Citalopram has demonstrated statistically significant improvement in anxiety among elderly patients when compared with placebo [23]. In a randomized, double blind, placebo-control study, the effects of citalopram on psychiatric and behavioral symptoms in Alzheimer's disease was evaluated. The study concluded that there was a significant decrease in anxiety symptoms after 9 weeks of citalopram use when compared with placebo [24••]. An open-label trial examined the impact of citalopram on anxiety symptoms, when Parkinson's disease patients are treated for depression. The study showed that 50% of the patients whose depression responded had a statistically significant decrease in anxiety symptoms. The same study reported that 70% of the patients reported only mild adverse events, with no serious adverse events [25]. Special consideration has to be taken when citalopram is prescribed for elderly patients with cardiovascular problems. Due to the propensity to cause abnormal cardiac conductivity, the dose of citalopram should not be higher than 40 mg/day in those under 65 years of age, and no higher than 20 mg/day in individuals over 65 [26, 27].

Sertraline is FDA-approved for the treatment of panic disorder and social anxiety disorder and has demonstrated effectiveness over worry symptoms when compared with CBT in the elderly [28]. In a randomized single-blinded trial, sertraline was compared with buspirone in the treatment of GAD in the elderly. Both medications appear to be well-tolerated and have good efficacy. There was no report of any serious adverse events during an 8-week period [29]. Sertraline may also improve anxiety symptoms and executive function in stages III or IV cancer patients [30].

Paroxetine is an FDA-approved SSRI for use in generalized anxiety disorder and panic disorder; however, it has been associated with more weight gain [31]. Paroxetine is the SSRI with the most anticholinergic

side effects which may lead to dry mouth, constipation, blurry vision, urinary retention as well as confusion in older individuals [32]. Additionally, paroxetine is a potent inhibitor of the cytochrome P450 2D6 hepatic pathway and therefore has considerable potential for drug interactions with patients taking other medications [33]. Fluoxetine, which is also FDA-approved for panic disorder as well as social anxiety disorder, and fluvoxamine are also both significant inhibitors of select P450 hepatic pathways [34, 35]. For these reasons, these SSRIs may not be optimal in late-life anxiety.

Common side effects from SSRI use in both general adults and the elderly may include gastrointestinal distress, insomnia, sexual side effects, somnolence, and headaches. In the elderly, upper gastrointestinal tract bleeding was nine times more common over 3 months in patients on an SSRI and a nonsteroidal anti-inflammatory medication than in a control group not on those medications. Additionally, a twofold increase in bone mineral density loss and hip fractures with use of SSRIs has been documented [36•, 37]. Hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is more frequently seen in elderly SSRI users. Table 1 shows the SSRIs recommended for use in anxiety in the elderly.

Serotonin and norepinephrine reuptake inhibitors (SNRIs)

Venlafaxine is FDA-approved for GAD and social anxiety disorder and has been found effective for treatment of anxiety in the elderly [38]. Similar to the side effect profile in SSRIs, sexual side effects are seen with venlafaxine, as well as sweating. In a randomized placebo-controlled trial study of adult subjects with generalized anxiety disorder, escitalopram was compared with venlafaxine. The two drugs showed equal efficacy, but there was a significantly increased rate of discontinuation due to secondary side effects for venlafaxine [39]. Venlafaxine also showed statistically significant increase in systolic and diastolic blood pressure, after 8 weeks of treatment [39]. These findings may indicate that SSRIs such as escitalopram may be a better tolerated first-line treatment over SNRIs in the elderly patient with cardiovascular disease.

Duloxetine is FDA-approved for GAD and had and has similar efficacy and side effect profile to SSRIs [40]. Additionally, blood pressure effects were not as significant as with venlafaxine [41]. Side effects include liver abnormalities. Although this risk is low, duloxetine should not be considered in patients with hepatic impairment. Excessive sweating as well as urinary retention, although infrequent, is a concern in the elderly [42]. Table 2 lists SNRIs and other antidepressants recommended for use in anxiety in the elderly.

Tricyclic/tetracyclic antidepressants (TCAs)

Tricyclic and tetracyclic antidepressants (TCAs) are effective in the treatment of anxiety disorders, such as panic disorder, GAD, and social anxiety

Table 1. Serotonin-specific reuptake inhibitors (SSRI) recommended for anxiety in the elderly

Drug (brand)	Formulation	FDA indications in anxiety	Starting dose	Titration	Dosage range	Side effects
Escitalopram (Lexapro)	5, 10, 20 mg oral solution 1 mg/ml	Generalized anxiety disorder (GAD)	10 mg/day	Usually not necessary	5–20 mg/day	Insomnia, nauseas, hyperhidrosis, fatigue, somnolence, decreased libido, anorgasmia ejaculation disorders
Citalopram (Celexa)	10, 20, 40 mg oral solution 10 mg/5 ml	None	10 mg	Increase to 20 mg after 7 days as tolerated	10–20 mg	QTc prolongation at doses >20 mg, nausea, vomiting, dry mouth, headache, somnolence, insomnia, sweating, tremor, diarrhea, sexual dysfunction, SIADH
Sertraline (Zoloft)	25, 5, 20,100 mg oral 20 mg/ml	Panic disorder, social anxiety disorder, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD)	12.5–25 mg/day	Increased by	12.5–25 mg every 2–3 days as tolerated to target dose	25–200 mg/day
Headache,		somnolence, insomnia, diaphoresis, diarrhea, sexual dysfunction				

Table 2. Serotonin and norepinephrine reuptake inhibitors (SNRI) and other antidepressants recommended for anxiety in the elderly

Drug (brand)	Formulation	FDA indications in anxiety	Starting dose	Titration	Dosage range	Side effects
Desvenlafaxine (Pristiq)	50–100 mg	None	50 mg every other day	Increase to 50 mg/day after 4–7 days	50 mg every other day to 50 mg every day	Nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, anxiety, sexual dysfunction, orthostatic hypotension, hypertension, hyponatremia, elevated lipids
Duloxetine (Cymbalta)	20, 30, 60 mg	GAD	20 mg/day	Increase by 20 mg after 7 days	20–60 mg	Nauseas, dry mouth, constipation, poor appetite, diarrhea, headache, insomnia, somnolence, fatigue
Venlafaxine (Effexor)	25, 37.5, 50, 75, 100 mg XR 37.5, 75, 150 mg	GAD, social anxiety disorder, panic disorder	IR 25 mg XR 37.5 mg/day	IR: increase by 25 mg every 4–7 days as tolerated to 25 mg tid; if response is inadequate after 3 more weeks, increase slowly to 75 mg tid XR: increase to 75 mg (target dose) after 4–7 days; may need to increase to 150 or 225 mg if response is inadequate	IR 50 mg tid XR 150 mg/day	Headache, dizziness, insomnia, hot

Table 2. (Continued)

Drug (brand)	Formulation	FDA indications in anxiety	Starting dose	Titration	Dosage range	Side effects
flush, hyperhidrosis, nausea						
Vortioxetine (Trintellix)	5, 10, 20 mg	None	5 mg/day	May increase to	10 mg/day	5–10 mg/day
Nausea, constipation, vomiting						
Mirtazapine (Remeron)	Tablets 7.5, 15, 30, 45 mg OD tablets 15, 30, 45 mg	None	7.5 mg qpm	Increase	7.5–15 mg every 1–2 weeks	7.5–45 mg/day
Somnolence, increased appetite with weight gain, increased serum cholesterol, constipation, dry mouth						

disorder. TCAs commonly prescribed include imipramine, amitriptyline, nortriptyline, and desipramine. There are no specific studies of use of TCAs in the elderly for anxiety. Extrapolation from adult studies suggests that TCAs may be helpful in the elderly [43]. TCAs, such as amitriptyline, also play a role in the treatment of neuropathic pain and headaches. Side effect profiles including anticholinergic, adrenergic, as well as cardiac conduction effects significantly limit use in older adults. Anticholinergic side effects may include orthostatic hypotension, falls, urinary retention as well as confusion. Because of significant side effect and safety considerations, TCAs are not recommended as a primary treatment option of anxiety in elderly patients.

Monoamine oxidase inhibitors (MAOIs)

MAOIs such as tranylcypromine and phenelzine have long been efficacious in treatment-resistant depression [44]. In adult studies, they have also been found to be efficacious in panic and social anxiety disorder

[45]. Caution should be used when extrapolating these results for the elderly given risk of orthostatic hypotension, falls, and hypertensive crisis. MAOIs are not recommended in the elderly for the primary treatment of anxiety.

Mirtazapine

No published studies have focused exclusively on late-life anxiety disorders and mirtazapine. However, one study [46] focused on mirtazapine use in post-traumatic stress disorder (PTSD) in older individuals with a mean age of 59. In this study, mirtazapine was found to be efficacious for PTSD in this age group. Mirtazapine is recommended in the elderly given its safe side effect profile and minimal drug-drug interaction. In addition, side effects can be used to our advantage as mirtazapine can help with insomnia and increase appetite in patient with weight loss. Patients with anxiety and difficulty with sleep or appetite can benefit tremendously from mirtazapine and it can be considered as a safe treatment option.

Vortioxetine

Vortioxetine is a new antidepressant with anxiolytic effects [47]. It is a serotonin modulator and stimulator that not only enhance serotonin activity but also increases the levels of norepinephrine and dopamine in ventral and medial prefrontal cortexes in rat models [48]. Vortioxetine is well-tolerated in elderly patients. When compared with placebo and duloxetine, nausea was the most common side effect in vortioxetine [49••]. Vortioxetine also showed significant improvement in cognition in patients with Major Depressive Disorder associated with previous cognitive decline [49••, 50]. Additionally, vortioxetine appears to enhance contextual and episodic memory and reverse memory deficits in the animal models [50, 51]. Given its favorable side effect profile, improvements in cognition as well as favorable outcome in clinical trials focused on elderly depressed subjects, vortioxetine can be a useful treatment option of anxiety in the elderly.

Buspirone

There are no randomized controlled trials evaluating buspirone for treatment of anxiety in the elderly. However, extrapolation from adult studies indicates that this could be a potential valuable adjunct for anxiety disorders [52, 53]. Buspirone has been found to be efficacious in GAD with less side effects than benzodiazepines. In fact, there are several case reports indicating it can be helpful in agitation and anxiety in patients with dementia [54, 55]. Buspirone does not cause respiratory

depression, cognitive impairment, or falls. However, it may have higher discontinuation rates, perhaps due to longer lag time to effectiveness.

Benzodiazepines

Benzodiazepines are commonly used in adults with anxiety disorders as adjunctive treatment when a patient is started on an antidepressant, such as an SSRI or SNRI. The goal is usually for efficacy in the short-term while the antidepressant is given time to take effect. In the elderly population, however, the risks often outweigh the benefits and they need to be used with caution. If absolutely needed, it is recommended that the physician prescribes lorazepam, oxazepam, or temazepam as these do not have active metabolites because they are metabolized by conjugation only. Benzodiazepine use in the elderly can lead to falls [56], hip fractures [57], and cognitive impairment [58, 59]. More recent studies have even found possible links between benzodiazepine use and dementia [60].

Antipsychotics

First-generation antipsychotics are generally avoided in the elderly due to significant side effects and safety issues. However, atypical antipsychotics are frequently prescribed off-label in the elderly to treat behavioral and psychiatric symptoms, especially in nursing homes [61]. It should be noted that there is a black box warning for both typical and atypical antipsychotics in the elderly with dementia due to increased mortality rates [62]. Although atypical antipsychotics are not FDA-approved for the treatment of anxiety disorders in the general population, there is some evidence to support their off-label use in select situations.

Out of all the atypical antipsychotic medications, quetiapine has shown efficacy in the treatment of GAD [63]. Pooling several clinical trials, it was found that quetiapine was better than placebo in both the maintenance and treatment of GAD [64]. Although not as strong as for monotherapy, there are also some studies that support quetiapine as an adjunctive therapy [65]. Special consideration must be paid to dosing when using quetiapine adjunctively. Co-administration with fluvoxamine will increase serum quetiapine levels [66]. It should be noted that although the use of quetiapine may be effective, there is not enough safety data for its use as GAD monotherapy, and longer-term studies still need to be done to be approved as an indication by the FDA.

Evidence for use of atypical antipsychotics to treat other anxiety-related disorders is less robust. In particular, an Agency for Health Care, Research and Quality (AHRQ) review found that they may be beneficial in both obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD). It found that studies of both risperidone and quetiapine have shown significant effects when used as augmentation to treatment with

SSRIs [64]. In head-to-head studies of augmentation treatment, there was no significant difference between olanzapine and risperidone with an SSRI, while quetiapine has been shown to have better efficacy than ziprasidone as an adjuvant [64]. The same AHRQ review on antipsychotic medications for treating PTSD found evidence supporting risperidone, olanzapine, and quetiapine as significantly superior to placebo [64].

Despite these results, the use, tolerability, and safety profile of antipsychotics has not been well-studied in elderly patients with anxiety. Furthermore, their use warrants particular concern as many atypical antipsychotics may be associated with changes in metabolic function, and treatments that do not potentially alter endocrine status are preferred. Risk of death associated with the use of antipsychotic medication in cognitively impaired elderly also should preclude their use. In the long-term, antipsychotics may also increase osteopenia and bone loss which can be profoundly detrimental in the elderly. They should not be considered a typical treatment regimen of anxiety in the elderly.

Mood stabilizers

There is minimal evidence for the use of mood stabilizers in anxiety disorders, especially in the elderly. In addition, most studies of mood stabilizers in the elderly involve bipolar disorder as opposed to anxiety disorders and there are many limitations due to small sample size. Even lithium, which is one of the most well-known mood stabilizers, has minimal and mixed results that are not directly related to anxiety [67–69].

Anticonvulsant medications are another genre of drugs commonly used as mood stabilizers. There are several studies that support carbamazepine and lamotrigine in the treatment of post-traumatic stress disorder (PTSD), but results have been mixed with the use of valproate for PTSD [70]. Valproate has also shown some effectiveness in both panic disorder and social anxiety [70]. Lamotrigine has demonstrated studies that support its use in PTSD, panic disorder with agoraphobia, and unipolar depression with comorbid anxiety [70–72]. Despite these finding in adult patients, anticonvulsants have significant side effects, drug interactions, and safety issues that can potentially affect older individuals. Cognitive slowing, tremor, liver abnormalities, rash, and sedation can be disabling to elderly individuals. In general, these medications should not be used first-line in geriatric patients with anxiety disorders given side effect profiles.

Beta-blockers

Beta-blockers are not commonly used in psychiatric treatment and are associated with development of psychiatric symptoms such as depression, sedation, and fatigue [73]. While there is evidence to support the use of beta-blockers to treat performance anxiety, their use is not indicated to treat other forms of anxiety [74]. Several case studies have shown metoprolol may induce anxiety in elderly patients, which improves or resolves with discontinuation of the drug [75]. One thought is that beta-blockers such as metoprolol and propranolol are lipophilic

and can thus cross the blood-brain barrier [75, 76]. These lipophilic drugs are also metabolized by the liver, which is an important consideration in elderly patients with comorbid heart or liver conditions as it can increase their circulating levels [76]. In addition, there are several other psychotropic medications that can affect beta-blocker efficacy and side effects. SSRIs, for example, can increase plasma concentrations of beta-blockers; meanwhile, TCAs can exacerbate their hypotensive effects [77]. Beta-blockers are therefore not recommended for use in late-life anxiety disorders.

Conclusion

In conclusion, there are very few studies examining pharmacological management of anxiety in the elderly. Anxiety disorders will become prevalent in older adults and those with medical and neurodegenerative illnesses as this population continues to grow. Given the differences in pharmacokinetics, metabolism, and vulnerability to medication side effects in the elderly, more randomized controlled trials will be needed to better understand the best anxiety treatment options for this group of Americans.

Compliance with Ethical Standards

Conflict of Interest

Katherine Camfield, Caroline Cruz-Ortiz, and Sindy Jaramillo declare that they have no conflict of interest.
Elizabeth Crocco reports grants from Otsuka Pharmaceutical Development & Commercialization, Inc; grants from Avanir Pharmaceuticals; personal fees from Mantovani Foundation, Milan, Italy; personal fees from Primed; and personal fees from Baptist Health, outside the submitted work.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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