F1000Prime REPORTS

Published: 05 January 2015

Managing anxiety associated with neurodegenerative disorders

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F1000Prime Reports 2015, **7**:05 (doi:10.12703/P7-05)

Abstract

Anxiety is a common symptom among patients with cognitive impairment. The presence of anxiety is correlated with poorer outcomes; despite this, there is limited research on anxiety related to neurodegenerative disorder. In this article, we discuss the prevalence of anxiety and factors involved in the etiology of anxiety in patients with diagnosed neurodegenerative disorders and related states of cognitive impairment as well as the evidence for currently available methods of evaluating and treating these symptoms. Specific treatments are highlighted in light of current evidence, followed by a discussion of the difficulties inherent in the study and treatment of anxiety in this population.

Introduction

Anxiety is a common symptom among patients with cognitive impairment, occurring in a majority of patients with dementia of the Alzheimer's disease (AD) type [1] and 10% to 45% of patients with mild cognitive impairment (MCI) [2,3]. It is the third most common neuropsychiatric symptom of MCI [4], and there is some indication that the presence of anxiety in MCI increases the risk of progressing to AD [5–7]. Neuropsychiatric symptoms (including anxiety, depression, psychosis, and agitation) are often the first signs of cognitive disorders and are correlated with faster progression to dementia [4,8]. Anxiety is often comorbid with non-AD dementias, particularly frontotemporal dementia, semantic dementia, and non-fluent aphasia [9,10]. The presence of anxiety has also been correlated with disability in social functioning independent of age [11]. Treatment remains difficult in these populations because of increased medical comorbidities, medication interactions, and cognitive side effects.

Underlying factors and pathophysiology of anxiety in neurocognitive disorders

Anxiety in patients with neurodegenerative disorders involves multifaceted and variable factors. Adding to this difficulty, anxiety is a general term that encompasses multiple symptoms and syndromes, and studies differ on criteria used. Patients with neurodegenerative disorders who present with symptoms of anxiety often have multiple potentially contributory medical comorbidities or possible underlying primary anxiety disorder (or both) prior to diagnosis of a neurodegenerative condition. Thus, both studying the pathophysiology of anxiety in neurocognitive disorders and applying the results of such studies to the care of patients are often difficult.

Anxiety is a consequence of multiple underlying and overlapping factors, including environment, physical state, underlying brain disease, heightened vulnerability due to age and cognitive decline, and psychological/existential issues. Biologically, anxiety is often conceptualized as a complex interaction between multiple systems within the brain, including the prefrontal cortex, amygdala, ascending norepinephrine and serotonergic pathways, and the hypothalamic-pituitary-adrenal axis among other systems involved in emotional processing, fear conditioning, and memory [12–15]. There is limited evidence as to the pathophysiology of increased anxiety in the specific context of neurodegeneration; the bilateral entorhinal cortex, amygdala, anterior parahippocampal gyri, left superior temporal gyrus, and insula have been implicated as playing a role in anxiety in the AD population [16–18], as has the salience network [19]. Anxiety is also frequently encountered in non-AD neurocognitive disorders, although the pathophysiology of anxiety in these conditions is even less

studied. Anxiety is also frequently comorbid with depression in this population [20], although any evidence for treatment of comorbid anxiety and depression in this population is limited to treatment of depression.

Evaluation of anxiety in neurodegenerative disorders

Initial symptoms

Signs and symptoms such as anxious or worried appearance, fearfulness, restlessness, tension, fidgeting, and sleep disturbance are non-specific, making a clear diagnosis of anxiety difficult [1,20]. As anxiety has a large cognitive component, it may be difficult to diagnose in patients with neurocognitive disorders. Comorbid medical conditions, particularly in patients with impaired communication skills, need to be evaluated with appropriate history, physical exam, and laboratory/imaging work-up. Anxiety can also manifest as agitation and aggression, particularly in patients with impaired communication or insight into their conditions. Interestingly, some studies suggest that greater insight into a diagnosis of dementia is correlated with increased anxiety and depression but that decreased insight is correlated with apathy [21].

Approach to evaluation

There are multiple ways to approach neuropsychiatric symptoms. In a recent article, a multidisciplinary panel suggests the "DICE" approach of describe, investigate, collaborate, and evaluate [22]. Using a behavioral approach, caregivers are asked to identify antecedents, specific behaviors, and consequences, followed by investigation into patient, caregiver, environmental, and cultural factors that could have contributed to the problem. This is followed by creation of an appropriate treatment plan based on behavioral interventions and appropriate treatment of physical concerns. Although this approach is likely to be used more in disruptive behaviors than anxiety, the behavioral basis could be helpful for anxiety, especially in a population that has decreased communicative ability.

One concern about such an approach is that caregivers can have a negative bias and over-report symptoms, particularly if the caregiver's own health is impaired [23]. Therefore, continued informed assessment by a clinician remains essential. As a first step in approaching the patient, appropriate history, mental status examination, physical examination, and diagnostic work-up are important to look for signs of endocrine (including thyroid, hypoglycemia, and pheochromocytoma), cardiovascular (tachycardia, arrhythmias, and anemia), respiratory (asthma, pneumonia, and hyperventilation), neurologic (seizures and focal syndromes), or other conditions contributing to or mimicking anxiety [24,25]. Substances must also be considered, particularly symptoms of alcohol withdrawal, intoxication with drugs of abuse, and anxiogenic medications. Although a full review of medical conditions and substances that can cause or mimic anxiety is beyond the scope of this article, it is important to review the list of medications (including over-the-counter medications, supplements, caffeine, recreational substances, and herbal treatments), which may have direct anxiogenic effects or cause symptoms that are similar to the symptoms of anxiety. If the patient has a known illness that can contribute to anxiety, such as asthma, or has been taking medications that can cause anxiety (such as sympathomimetics), then consideration should first go toward managing those conditions or medications. Although evidence is limited, there is some indication that certain "medical mimics" of anxiety may be experienced differently than primary anxiety; for example, one study indicated that patients with pheochromocytoma experienced symptoms similar to anxiety but without the severe apprehension, fear, or agoraphobia of patients with primary anxiety disorders [26]. However, such a distinction is made more difficult by patients with neurocognitive disorders, who may not be able to adequately explain their inner experiences.

Clinicians can use a behavioral-based method similar to the components in the DICE approach, first exploring both the symptoms and the context, then considering comorbidities, possible explanations, and contributing/reinforcing medical, environmental, and cultural factors. To increase recognition and diagnosis, multiple scales have also been used to determine neuropsychiatric symptoms in patients with cognitive impairment, including the behavioral pathology in AD (BEHAVE-AD), neuropsychiatric inventory (NPI), behavioral rating scale, and the NPI-clinician rating scale (NPI-C) [4]. These scales are useful for identification of potential anxiety, although their utility in choosing an appropriate treatment is unclear.

Treatment to overview

We will briefly review common treatments for anxiety in individuals with diagnosed cognitive impairment. This does not include treatment of underlying conditions that present as anxiety, which is a large topic beyond the scope of this review. A common theme during this discussion is lack of good data for use in the cognitively impaired population, especially in regard to pharmacologic approaches; similarly, there is a clear lack of adequate understanding of how each pharmacologic target is related to the underlying pathophysiology of neurodegenerative disorders.

Pharmacologic approaches

Antidepressants

Antidepressants, as a general class, have been used for depression in the setting of neurodegenerative disorders, though with some controversy in regard to their efficacy [27]; evidence of their efficacy for anxiety in this population is even less strong [4]. As with cognitively intact patients, serotonergic depressants are the most studied for anxiety. Although data are limited, selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors can be considered valid options for treatment, especially since they do not have many of the problems associated with other anxiolytics and have been found to be efficacious in those with anxiety disorders without dementia. However, it is important to note that many of the tricyclics are listed in the Beers List (Beers Criteria for Potentially Inappropriate Medication Use in Older Adults) as "avoid" because of their anticholinergic and sedating properties [28].

Benzodiazepines

Benzodiazepines have limited use in the older or cognitively impaired population because of cognitive side effects, increased risks of falls, paradoxical agitation, and tolerance [29,30]. All benzodiazepines are listed on the Beers List as "avoid" for agitation and insomnia, and it is noted that smaller doses may be as effective and safer in the older population [28]. When used, benzodiazepines should be used at low doses in a time-limited fashion and with close follow-up and monitoring.

Cholinesterase inhibitors

There have been limited but encouraging data on the effect of cholinesterase inhibitors on behavioral symptoms of neurodegenerative disorders, including anxiety [31]. A few trials have indicated that donepezil may have some beneficial effect on anxiety and agitation [32]. Rivastigmine was found to have improvement in anxiety in one open-label observational study [33], although other studies report improvement in functioning but with noticeable side effects [34]. Galantamine has been associated with improved functioning and behavior, although effects on anxiety itself have not been reported [35,36]. Cholinesterase inhibitors are also frequently used for neuropsychiatric symptoms associated with dementia with Lewy bodies because of prominent cholinergic deficits, although it is unclear whether this would be helpful for anxiety specifically [37,38].

Memantine

Memantine is an antagonist of N-methyl-D-aspartate (NMDA) receptors approved for treatment of moderate to severe dementia. It has been shown to have some possible anxiolytic effects in mice models and has been suggested as an adjunctive treatment for mood and anxiety disorders, but with disappointing results thus far [39,40]. There are limited data on its effect on anxiety when used for dementia.

Buspirone

Buspirone is an anxiolytic medication that is a partial agonist at the serotonin $5HT_{1A}$ receptor; it is also an antagonist at the dopamine D2 autoreceptor and may have weak affinity to $5HT_2$ receptors. Its benefits include a low potential for dependence and many of the side effects of benzodiazepines, and it has shown some benefit in the behavioral disturbances in neuropsychiatric conditions [41,42]. There are some reports of anxiolytic effect in dementia, although most evidence is in patients with agitation [41,43].

Melatonin

Melatonin is a pineal-secreted neurohormone that is important for maintenance of a normal circadian rhythm. It is frequently used for sleep, although a recent Cochrane review concludes that evidence for efficacy in AD is limited [44]. Melatonin receptor type 2 (MT2) receptors have been found to increase gamma-aminobutyric acid (GABA) levels in several brain regions [45], and one study indicated that initiation of melatonin helped facilitate benzodiazepine discontinuation [46]. Further studies into the appropriate use and long-term side effects of melatonin use in cognitively impaired patients are required.

Others

Beta adrenergic receptor antagonists are sometimes used in the treatment in anxiety and have also been used to treat aggression in neuropsychiatric patients and patients with intellectual disabilities [47]. However, they have adverse side effects such as bradycardia and hypotension, and there is concern for limited efficacy and diminishing benefits over time [48]. Antihistaminergic medications are also used for anxiety but, owing to likely confusion and sedation, are clearly not preferred in the cognitively impaired or older population [28].

Non-pharmacologic approaches

Non-pharmacologic approaches to anxiety in the setting of cognitive impairment include cognitive therapies, behavioral therapies, cognitive-behavioral therapies, environmental approaches, and diet and exercise approaches. Strong studies of these approaches for comorbid anxiety and dementia are lacking; however, cognitive-behavioral approaches to anxiety in general have a strong evidence base and therefore seem promising for cognitively impaired patients if their level of functioning is such

that they are able to participate in the treatment. Environmental approaches, including music, consistency in routine, orienting cues, distraction reduction, and appropriate level of stimulation, have been studied and have shown good effect for neuropsychiatric symptoms in general [49]. Diet and exercise approaches have less evidence but may have benefits because of improved health and increased activity.

Non-pharmacologic somatic treatments, in particular electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS), have been used and studied in geriatric populations. However, electroconvulsive therapy is not typically recommended for anxiety, and the role of rTMS for anxiety in any population is still unclear [50–52]. One possible exception is the established utility of ECT in Parkinson's disease with psychosis and comorbid anxiety, which was reported to be helpful in two cases [53].

Conclusions

Anxiety is a prevalent and impairing comorbidity among patients with cognitive disorders. Appropriate evaluation and work-up are necessary, followed by consideration of both non-pharmacologic and pharmacologic treatments. The combination of limited data and high risk of adverse effects makes treatment of anxiety difficult in the cognitively impaired and older populations. Difficulties in studying this population include typically advanced age, comorbid medical problems, frequently murky correlation between clinical signs and underlying pathology, concern for ability to obtain consent, medication interactions, concern for harm in placebo groups without active treatment, and difficulty obtaining an appropriately representative and significantly large sample size. Anxiety is also difficult to both study and treat in those who are not able to express themselves, as it can manifest quietly (internal anxiety that is not recognized by caregivers) or explosively (in aggressive violence or unusual behaviors). As older patients are less likely to report mental health problems, "quiet" anxiety may be missed; on the other hand, it is difficult to determine whether aggression and agitation are due to anxiety, and therefore it is difficult to draw conclusions about treatment of "explosive" anxiety. Further study into valid measures of differing types of anxiety in severely cognitively impaired patients, particularly in regard to neuropsychological evaluation and biomarkers, could lead to improved recognition and appropriate diagnosis.

Clinicians are currently able only to manage symptoms of neurodegenerative disorders; as reflected in this article, even these symptomatic treatments have limited evidence for use in anxiety. In practice, we often recommend use of cholinesterase inhibitors or memantine first because of indication for the primary disorder, relatively low side effect profile, and (particularly in the case of cholinesterase inhibitors) some evidence of positive effect on anxiety. If anxiety remains problematic, a trial of SSRIs or buspirone would be the next step. Benzodiazepines, beta-adrenergic antagonists, tricyclics, and antihistaminergic medications are often the last to be considered, because of side effect profiles, but may be useful in select cases with appropriate monitoring. The geriatric psychiatry mantra of "start low and go slow" is clearly applicable to this patient population. In addition to medications, environmental approaches, especially consistency in routine, orienting cues, appropriate level of stimulation, and evaluation of triggers, are recommended in almost all cases. Referral to psychotherapy is limited to patients who can participate appropriately.

Current research seeks the ultimate goal of disease-modifying treatments, which are also the ultimate hope for treatment of neuropsychiatric symptoms such as anxiety. In the meantime, ongoing basic science research in both neurodegenerative and anxiety disorders, as well as clinical research into various pharmacologic and non-pharmacologic treatments, will hopefully improve insight into optimal treatment.

Abbreviations

AD, Alzheimer's disease; DICE, describe, investigate, collaborate, and evaluate; ECT, electroconvulsive therapy; GABA, gamma-aminobutyric acid; MCI, mild cognitive impairment; NPI, neuropsychiatric inventory; rTMS, repetitive transcranial magnetic stimulation; SSRI, selective serotonin reuptake inhibitor.

Disclosures

Anand Kumar receives grants from the National Institutes of Health and an honorarium from the American Journal of Geriatric Psychiatry as associate editor. Brian P. Gomoll declares that he has no disclosures.

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