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Anxiety in dementia:

A critical review

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Abstract

Until recently, little attention has been paid to anxiety symptoms in dementia. However, anxiety is common in this population, and associated with poor outcome and quality of life. The current review examines the existing literature around three major themes: the definition of anxiety in dementia, the properties of available instruments for assessment, and the clinical characteristics of anxiety in this population. Defining anxiety in individuals with dementia is complicated by the overlap between symptoms of anxiety, depression and dementia, and by the influence of the source of information. Several instruments are available to assess anxiety in this population, including general neuropsychiatric instruments and two scales designed specifically for this purpose. The reliability of these instruments is acceptable, but their validity has not been sufficiently examined, and they may discriminate poorly between anxiety and depression. Anxiety may be higher in vascular dementia than in Alzheimer's Disease, and it decreases in the severe stages of dementia. It is associated with poor quality of life and behavioral disturbances, even after controlling for depression. Little is known, however, about its social and environmental correlates. Limitations of the existing literature and key directions for future research are discussed.

Keywords

Dementia; Alzheimer's Disease; Anxiety

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For the past 20 years, a growing body of literature has examined the assessment, prevalence, and treatment of neuropsychiatric and behavioral problems associated with dementia. Until recently, anxiety symptoms in dementia have received little attention (Shankar & Orrell, 2000). Anxiety, however, is common in this population, with prevalence estimates ranging from 5% to 21% for anxiety disorders (Chemerinski, Petracca, Manes, Leiguarda, & Starkstein, 1998; Ferretti, McCurry, Logsdon, Gibbons, & Teri, 2001; Forsell & Winblad, 1997; Skoog, 1993; Starkstein, Jorge, Petracca, & Robinson, 2007), and from 8% to 71% for anxiety symptoms (Ballard, Neill, O'Brien, McKeith, Ince, & Perry, 2000; Chemerinski et al., 1998; Lyketsos et al., 2001; Wands, Merskey, Hachinski, Fisman, Fox, & Boniferro, 1990). Anxiety is more common in individuals with dementia than in individuals without dementia (Bungener, Jouvent, & Derouesne, 1996; Hwang, Masterman, Ortiz, Fairbanks, & Cummings, 2004; Lyketsos, Steinberg, Tschanz, Norton, Steffens, & Breitner, 2000; Porter et al., 2003; Wands et al., 1990), and it is associated with worse quality of life (QoL), problem behaviors, limitations in activities of daily living, nighttime awakenings and poorer neuropsychological performance, even after controlling for depression (Hoe, Hancock, Livingston, & Orrell, 2006; McCurry, Gibbons, Logsdon, & Teri, 2004; Starkstein et al., 2007; Teri et al., 1999). Anxiety in dementia has also been associated with future nursing home placement, suggesting that it represents a particularly burdensome problem for caregivers (Gibbons, Teri, & Logsdon, 2002).

In the past few years, researchers have begun to address anxiety symptoms in dementia. Several reviews have been published, providing useful updates and suggesting future directions (Mintzer, Brawman-Mintzer, & Mirski, 2000; Shankar & Orrell, 2000; Yesavage & Taylor, 1991). These reviews, however, are brief, address only limited aspects of the topic and are now several years old. Given recent developments in assessment and conceptual approaches, an updated and comprehensive review is warranted. The current review focuses on three main topics, each of which answers a key question or set of questions and provides specific recommendations. We begin with a discussion of what is the best way to define anxiety in dementia. This discussion sets a foundation for our second section, where we critically review the instruments that have been used to assess anxiety in dementia, concluding with recommendations for assessment. Third, we examine the clinical characteristics of anxiety in dementia. We conclude by a discussion of existing limitations and recommendations for future research.

1. Search strategy

Initial searches in PubMed and PsycINFO were conducted using the subject words *dementia* combined with *anxiety*. In PsychINFO, we also searched the combination of subject words *dementia* and *neuropsychiatry*. These two databases were chosen because they are representative of the literature published on this topic and have been used in prior reviews of anxiety in caregivers of individuals with dementia (Cooper, Balamurali, & Livingston, 2007) and anxiety and QoL (Olatunji, Cisler, & Tolin, 2007). Additional articles were found through cross-references. Based on this initial search, 513 titles and abstracts were examined. A majority of articles (N=388) pertained to anxiety and dementia separately, rather than to anxiety in dementia, and were excluded from further review. The remaining 125 articles were reviewed with attention to the following inclusion criteria: (a) the article was in English, (b) the study presented original empirical research, (c) the sample, or at least a subset of the sample, consisted of participants who were diagnosed with dementia, (d) when the total sample included participants with and without dementia, sufficient data were available to evaluate the effect of interest in the dementia group, (e) anxiety symptoms or disorders were assessed, (f) the sample size was larger than 20, and (g) for factor analytic studies, the sample size was larger than 100, which has been suggested as a minimum for studies of this type (Guadagnoli & Velicer, 1988). Seventy-four studies met these criteria. The subsets of studies selected to address each

of the main topics of this review (definition, assessment, and clinical characteristics) are described in each section below.

2. Defining anxiety in dementia

As already noted, the rate of anxiety disorders and symptoms in dementia varies dramatically from study to study, suggesting that there is a lack of consensus about how to define and conceptualize anxiety in this population. Several issues complicate this question, including the distinction between symptoms of anxiety and symptoms of dementia, the overlap between anxiety, depression, and agitation, and what constitutes the best source of information (e.g., patient, caregiver). We now examine each of these questions in turn.

2.1. Differentiating anxiety from dementia

One of the difficulties in studying anxiety in dementia is the symptom overlap between the two conditions. For Generalized Anxiety Disorder (GAD), in particular, possible symptoms include restlessness, being easily fatigued and difficulty concentrating, all of which can occur in dementia without the presence of an anxiety disorder. Unfortunately, the hallmark of GAD, excessive anxiety or worry that is difficult to control, cannot always be assessed reliably in individuals with dementia, particularly those with expressive or receptive language difficulties. Thus, a difficult question for researchers and clinicians is whether anxiety symptoms that could potentially be accounted for by the presence of dementia should be used to diagnose an anxiety disorder.

To address this question, the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV; American Psychiatric Association, 2000) provides general guidance but few specific suggestions: the deciding factor in determining whether a set of symptoms contribute to an independent psychological disorder is whether the symptoms can be explained by the *direct physiological effects* of the disease. In the case of anxiety and dementia, several factors suggest that such a direct relationship is possible. First, the neural degeneration responsible for the cognitive decline observed in dementia could also affect limbic structures associated with emotional regulation. Second, anxiety is more common in individuals with dementia than in individuals without dementia, and, as we will see, the prevalence of anxiety varies by dementia type. Third, as already mentioned, dementia symptoms overlap substantially with anxiety symptoms. Determining whether a direct causal relationship exists for a given patient, however, is exceedingly difficult. Several possible strategies have been used to address this difficulty:

- In some studies, the potential overlap between symptoms of anxiety and symptoms of dementia has been largely ignored: DSM-IV criteria or measures of anxiety symptomatology have been used as usual, regardless of etiology (e.g., Ferretti et al., 2001). Only symptoms that are clearly the result of a comorbid medical condition (e.g., heart thumping for a patient with atrial fibrillation) were discounted (Shankar, Walker, & Frost, 1999). This approach has the advantage of avoiding subjective determination of the cause of anxiety symptoms. It raises the risk, however, of inflating the severity of anxiety symptoms and the prevalence of anxiety disorders.
- Some instruments (which will be reviewed in the next section), designed specifically for the assessment of neuropsychiatric symptoms in dementia, include only items that are less likely to overlap with symptoms of dementia. At the same time, they include items that are not typically assessed in the general population but that may be common in anxious individuals with dementia (e.g., fear of being alone).
- Using an empirical approach, Starkstein et al. (2007) sought to determine which symptoms best distinguish individuals with dementia with and without GAD. They found that, in addition to excessive anxiety/worry that is difficult to control,

restlessness, irritability, muscle tension, fears and respiratory symptoms independently predicted GAD diagnosis. Based on these findings, they suggested revised criteria for GAD in individuals with dementia consisting of: (a) excessive anxiety/worry that is difficult to control (criteria A and B of the DSM-IV), and (b) three of the aforementioned five symptoms.

Out of these three potential strategies, the first one, which ignores the potential overlap between symptoms of anxiety and dementia, is likely to inflate rates of anxiety disorders and symptoms. Selecting items that minimize potential overlap is a preferred approach. Using revised diagnostic criteria for anxiety disorders in dementia, as has been proposed by Starkstein et al. (2007), is also promising. Such an approach, however, should be based on consensus guidelines from experts in the field in addition to empirical data, as exemplified by the provisional diagnostic criteria for depression in Alzheimer's Disease (AD; Olin, Katz, Meyers, Schneider, & Lebowitz, 2002a; Olin et al., 2002b).

2.2. Differentiating anxiety from agitation and depression

One important question regarding anxiety symptoms in dementia is whether they should be considered as a separate clinical entity or as part of a broader syndrome. Some authors have suggested that there is strong overlap between anxiety and agitation (Yesavage & Taylor, 1991), and that perhaps agitation may be a symptom of generalized anxiety (Mintzer & Brawman-Mintzer, 1996). To determine whether anxiety is distinct from other neuropsychiatric symptoms in dementia, we reviewed factor analyses pertaining to this question. Table 1 lists the six studies included in our review. Four studies used orthogonal rotations, constraining factors to be uncorrelated, which may result in the appearance of spurious and unreliable factors (Guadagnoli & Velicer, 1988). The other two studies used oblique rotations. Regarding the overlap between anxiety and agitation, two studies (Harwood, Ownby, Barker, & Duara, 1998; Mirakhur, Craig, Hart, McLlroy, & Passmore, 2004) found anxiety and agitation to load on the same factor, while three others (Aalten et al., 2003; Cummings, McRae, & Zhang, 2006; Frisoni et al., 1999), including the two studies that used oblique rotations (Cummings et al., 2006; Frisoni et al., 1999), found them to load on separate factors. Moreover, one study that explicitly examined the relationship between anxiety and agitation found only a modest correlation (r=.41), suggesting that the two constructs are not equivalent (Twelftree & Qazi, 2006). Thus, the existing evidence provides more support for the distinctiveness of anxiety and agitation than for their equivalence.

Another possibility is that anxiety is confounded with depression in individuals with dementia. In cognitively intact older adults, depression and anxiety are comorbid but form distinct constructs (Schoevers, Deeg, van Tilburg, & Beekman, 2005; Wetherell, Gatz, & Pedersen, 2001). In dementia, between 68% and 75% of individuals with dementia and GAD also meet criteria for a Major Depressive Disorder (Ferretti et al., 2001; Starkstein et al., 2007), and GAD is associated with greater depressive symptoms in AD (Chemerinski et al., 1998). Studies examining the validity of instruments designed to assess anxiety symptoms have found strong overlap between the two constructs (Gibbons, Teri, Logsdon, & McCurry, 2006), and controlling for depression sometimes, but not always, eliminates the association between anxiety and other variables (Harwood, Sultzer, & Wheatley, 2000; Hoe et al., 2006; McCurry et al., 2004; Orrell & Bebbington, 1996; Seltzer, Vasterling, & Hale, 1995; Teri et al., 1999). Factor analyses (see Table 1) have yielded contradictory findings: in three studies (Cummings et al., 2006; Frisoni et al., 1999; Mirakhur et al., 2004), anxiety and depression loaded on the same factor, while they belonged to distinct factors in two studies (Forsell, Jorm, & Winblad, 1993; Harwood et al., 1998). Finally, in one study (Aalten et al., 2003), anxiety loaded equally strongly on a depression/apathy factor and on a psychotic symptoms factor. Because the studies varied in more than one aspect (type of dementia, community sample vs. patients from memory clinic, oblique vs. orthogonal rotation, instrument used), it is difficult to ascertain which

variables contributed to these findings. In summary, the bulk of the evidence suggests that depression and anxiety are highly comorbid in individuals with dementia. Whether they form distinct constructs is unclear at this point, as existing studies provide conflicting evidence. The main limitation to providing a more definitive conclusion is that, despite its importance, no study to date has yet focused specifically on this question. Rather, the existing evidence is indirect and incidental.

2.3. What constitutes the best source of information to assess anxiety in dementia?

In the general population, the most common source of information to determine the presence of an anxiety disorder is the patient him- or herself. In dementia, this option may not always be optimal, as some patients have difficulty communicating and remembering their symptoms. To avoid these difficulties, some authors have chosen to rely exclusively on caregiver report. This strategy may work well for situations in which the core symptom is behavioral (e.g., avoidance in specific phobia). In the case of GAD, however, the core symptoms of worrying and difficulty controlling the worry are private in nature, and caregivers might not be aware of them, particularly if the relationship between patient and caregiver is strained. Moreover, as we have seen, some of the outward manifestations of anxiety (e.g., trouble concentrating) are highly confounded with symptoms of dementia. Thus, exclusive reliance on caregiver report may be the only choice when patients are too impaired to communicate effectively. In other cases, however, it would deprive the examiner of a valuable source of information.

Another possible approach is to collect information from multiple sources, including caregiver, patient, staff and medical records. This approach has long been used for the assessment of depression in dementia (Alexopoulos, Abrams, Young, & Shamoian, 1988), and also forms the basis of a recent measure of anxiety symptoms in dementia, the Rating Anxiety in Dementia scale (RAID; Shankar et al., 1999), which will be discussed in greater detail below. It has the advantage of offering a more comprehensive picture of anxiety symptoms. It has, however, the disadvantage of requiring the clinician to determine, in case of inconsistencies, which of the patient, caregiver or staff provides the most accurate picture.

2.4. Recommendations for defining anxiety in dementia

Existing studies have examined anxiety in individuals with dementia both as a set of diagnostic entities and as continuous measures of symptomatology. Both approaches can be useful and even complementary, for instance in treatment studies where patient selection is often based on diagnostic criteria and estimates of treatment effects on symptom severity. Given the overlap between symptoms of anxiety and symptoms of dementia, it is unclear whether traditional definitions of anxiety are adequate in this population. Modified criteria for GAD have been suggested (Starkstein et al., 2007), although they probably require expert consensus for greater validity and wide adoption. Given the private nature of core symptoms of anxiety (e.g., worry), defining anxiety based solely on behavioral observations or caregiver report may be insufficient.

3. Assessment

Articles describing instruments designed to assess anxiety in dementia, or providing information regarding the reliability and validity of such instruments, were reviewed and included in the present section. Thirteen studies were identified pertaining to four distinct instruments (Auer, Monteiro, & Reisberg, 1996; Cummings, 1997; Cummings, Mega, Gray, Rosenberg-Thompson, Carusi, & Gornbein, 1994; Fuh, Liu, Mega, Wang, & Cummings, 2001; Gibbons et al., 2006; Kang et al., 2004; Kaufer et al., 2000; LaBarge, 1993; Patterson, Schnell, Martin, Mendez, Smyth, & Whitehouse, 1990; Reisberg, Auer, & Monteiro, 1996; Reisberg, Borenstein, Salob, Ferris, Franssen, & Georgotas, 1987; Sclan, Saillon, & Franssen,

1996; Shankar et al., 1999). Two of these instruments were designed for the assessment of neuropsychiatric symptoms in general, and the other two for anxiety specifically.

3.1. General purpose neuropsychiatric instruments

Multiple instruments are available for assessing neuropsychiatric and behavioral symptoms in dementia, but only two of them include subscales that target anxiety. The Behavioral Pathology in Alzheimer's Disease Scale (BEHAVE-AD; Reisberg et al., 1996, 1987) comprises seven domains, each assessed based on a caregiver interview. The anxiety domain includes four items: anxiety regarding upcoming events, other anxieties, fear of being left alone, and other phobias. Thus, rather than inquiring about specific symptoms (e.g., sweating), the BEHAVE-AD asks the caregiver to make broad judgments about the presence of anxieties and fears. The anxiety score is obtained by adding the individual scores from each item. Estimates of interrater reliability have ranged from good (.60) to excellent (.89) across studies (Patterson et al., 1990; Sclan et al., 1996). Support for the usefulness of the BEHAVE-AD comes from studies showing decreases in anxiety scores after treatment for neuropsychiatric symptoms with olanzapine and risperidone (Moretti, Torre, Antonello, Cattaruzza, Cazzato, & Bava, 2004; Suh, Greenspan, & Choi, 2006). Construct validity has not been fully examined. In one study (Cummings et al., 1994), large correlations (between .60 and .66) were found between the anxiety domains of the Neuropsychiatric Inventory (NPI; Cummings et al., 1994) and BEHAVE-AD. Because overall neuropsychiatric symptoms were not controlled for, it is impossible to determine whether these large correlations result from good construct validity of the NPI and BEHAVE-AD anxiety scales or reflect the effects of a general factor (i.e., overall distress or disturbance). One factor-analysis of the BEHAVE-AD found that the two anxiety items loaded on a common factor with agitation (Harwood et al., 1998). Because the study had a relatively low sample size (N=152) and used an exploratory method with orthogonal rotation (see Table 1), results should be taken cautiously.

The Empirical BEHAVE-AD (E-BEHAVE-AD; Auer et al., 1996) is an extension of the BEHAVE-AD that does not rely on information provided by the caregiver. Rather, it consists of an informal interview with the patient alone, from which behavioral observations are used to score twelve items forming six domains. For the anxiety domain, two items are used: general anxieties and fear of being left alone. These two items have excellent interrater reliability (.86 and 1.00, respectively), and the anxiety score of the E-BEHAVE-AD correlates moderately (.41) with that of the BEHAVE-AD. Unfortunately, correlations between different domains of the two measures (e.g., anxiety from the E-BEHAVE-AD and depression from the BEHAVE-AD) were not reported in this study. Thus, similar to the relationship between the BEHAVE-AD and NPI, it is unclear whether the observed correlation is due to anxiety specifically or to a general factor such as overall distress or functioning.

The NPI (Cummings et al., 1994) comprises 10 domains, with a later version adding two additional domains (Cummings, 1997). The symptoms are assessed for the last 30 days and, as the BEHAVE-AD, the NPI is scored based on an interview with a caregiver. For each domain, the NPI begins with a screening question, followed by seven or eight more specific questions. For anxiety, the specific questions are: worrying about planned events; feeling shaky, unable to relax or tense; shortness of breath or gasping; butterflies in stomach or racing/pounding heart; avoidance of certain situations; becoming nervous when separated from caregiver; and other symptoms of anxiety. The caregiver is asked to rate the overall frequency (1-4) and severity (1-3) of anxiety symptoms, as well as distress to the caregiver (0-5). Frequency and severity are multiplied to yield a domain score.

Good interrater reliabilities for the anxiety domain have been reported for frequency (93.6% agreement) and severity (100% agreement), while test-retest reliabilities range from .64 to .71 (Cummings et al., 1994; Fuh et al., 2001). As noted before, large correlations have been

reported between the anxiety domains of the NPI and the BEHAVE-AD, but they provide little information about construct validity since the rate of overall neuropsychiatric symptoms was not controlled. Four factor analyses of the NPI have been conducted. In three of them (Cummings et al., 2006; Frisoni et al., 1999; Mirakhur et al., 2004), depression and anxiety loaded on the same factor, while in the last one (Aalten et al., 2003), anxiety loaded equally on a depression/apathy factor and on a psychotic symptoms factor (see Table 1).

Several alternate versions of the NPI have been developed. Due to its length (15 min or more) and its reliance on the clinician to complete the caregiver interview, the original NPI can be burdensome in general practice settings, where other aspects of the patient functioning in addition to neuropsychiatric symptoms must be assessed in a limited amount of time. A short version, the NPI-Q, includes only the screening question and the frequency and severity ratings (Kaufer et al., 2000). It is completed by the caregiver as a self-administered questionnaire, thus minimizing demands on clinician's time. Correlations between the anxiety domains of the NPI and the NPI-Q range from .82 to .84, suggesting good agreement. Similar to the NPI-Q, the Caregiver-Administered Neuropsychiatric Inventory (CGA-NPI; Kang et al., 2004) is a self-administered questionnaire completed by the caregiver, minimizing administration time. Unlike the NPI-Q, however, it includes all the original items of the NPI. There is also good agreement between the CGA-NPI and the original NPI for prevalence (κ=.62), frequency (r=.69), severity (r=.64) and caregiver burden (r=.61) of anxiety.

Other scales assessing neuropsychiatric symptoms have been developed that include anxiety items, including the Neurobehavioral Rating Scale (Levin et al., 1987), the Present Behavioural Examination (Hope & Fairburn, 1992) and the Gottfries-Brane-Steen scale (Gottfries, Brane, & Steen, 1982). These scales, however, do not provide anxiety subscores, and thus will not be reviewed here.

3.2. Instruments designed for assessing anxiety symptoms in dementia

Two scales have been designed specifically to assess anxiety or worry in dementia. The Worry Scale (LaBarge, 1993), a self-report measure for use in individuals with mild dementia, has good internal consistency (α=.85) and correlates strongly with measures of trait and state anxiety (.55 for both). However, it also correlates strongly with measures of depression (.66), and moderately with measures of state and trait anger (.32 and .31, respectively). Moreover, an examination of scale items reveals that they cover a wide range of coping and emotional responses to dementia, including anger ("I feel resentful and angry"), embarrassment ("I feel embarrassed"), and confidence in one's abilities ("I can handle changes in my life as they come").

The RAID (Shankar et al., 1999) was developed for use with persons with dementia. It includes 20 items, each scored on a 4-point scale. Several items inquire about worry (worry about physical health, finances, etc.), while others include sleep disturbance, irritability, and a number of somatic symptoms (palpitations, dry mouth, shortness of breath). The last two items, which are not included in the total score, inquire about phobias and panic attacks. Information is gathered about the patient's symptoms over the past two weeks from all available sources, including the patient, the caregiver, clinical observations and medical records. For each item, the clinician determines a single score based on all available information. A total score is obtained by adding the scores for the first 18 items. Scale items show fair to excellent interrater and test-retest reliability, and the scale has satisfactory internal consistency (α=.83). Moreover, RAID scores are higher for patients whose symptoms meet DSM-IV criteria for GAD, and a cutoff score of 11 provides a sensitivity of .90 and a specificity of .79 (Shankar et al., 1999). Because these findings are based on a single study (Shankar et al.) with a relatively small sample size (N=83), they should be interpreted cautiously. The RAID correlates with some but not all measures of anxiety, with correlations ranging from .16 to .62 (Gibbons et al., 2006;

Shankar et al., 1999). Its correlation with the Cornell Scale for Depression in Dementia (CSDD; Alexopoulos et al., 1988) is of a similar magnitude or even higher, ranging from .66 to .69 (Gibbons et al., 2006; Shankar et al., 1999). The substantial correlation between the RAID and the CSDD may be due to poor validity of one or both measures, symptom overlap and/or comorbidity (Gibbons et al., 2006).

3.3. Evaluation of assessment measures

Based on our discussion of the optimal way to define anxiety in dementia, several recommendations can be made to evaluate existing instruments. First, because it is unclear at this point whether anxiety is part of a broader syndrome (agitation or depression) in this population, it should be assessed independently. Second, instruments should focus on symptoms of anxiety that are less likely to be affected by the presence of dementia. Concentration difficulties, in particular, are not likely to discriminate well between anxious and non-anxious individuals with dementia (Starkstein et al., 2007). Third, instruments should whenever possible be scored based on information from multiple sources, including at least the patient him- or herself and a caregiver. Finally, instruments should have strong psychometric properties, i.e., reliability, validity and sensitivity to change.

We now evaluate the NPI, BEHAVE-AD, Worry Scale and RAID as measures of anxiety using these four criteria. First, all instruments purport to measure anxiety specifically (or, for the NPI and BEHAVE-AD, include a separate anxiety scale), thereby satisfying our first criterion. Our second criterion states that symptoms most likely to overlap with symptoms of dementia should be avoided. The three instruments use different strategies in this respect. The BEHAVE-AD asks the caregiver to determine the presence and severity of anxieties and fears without inquiring about specific symptoms. Although this strategy appears to avoid ostensible confounds, it shifts the responsibility of defining anxiety and distinguishing between symptoms of anxiety and symptoms of dementia to the caregiver. At the opposite end, the RAID takes a descriptive approach and assesses specific symptoms such as worry about upcoming events, irritability or palpitations. Some of these symptoms, however, could overlap with other medical or psychiatric conditions. The NPI takes an intermediate approach, assessing anxieties and fears as well as specific somatic symptoms (e.g., butterflies in stomach). The Worry Scale, which inquires mostly about subjective emotional states, is likely to minimize overlap with dementia symptoms. One common weakness is that none of the instruments includes items identified by empirical methods. None, however, includes loss of concentration, which would likely be difficult to disentangle from dementia.

Our third criterion recommends the use of multiple sources of information. Only the RAID fulfills this criterion, while the NPI and BEHAVE-AD rely only on caregiver report. The Worry Scale, which relies solely on self-report, can be used only with individuals with mild dementia, which limits its usefulness. Such an approach also ignores difficulties related to lack of insight, which is common in dementia, even in the mild stage (Derouesné, Thibault, Lagha-Pierucci, Baudouin-Madec, Ancri, & Lacomblez, 1999; Zanetti et al., 1999).

Regarding our fourth criterion, all three instruments have acceptable reliability, but inadequate or undocumented construct validity. The RAID and Worry Scale correlate as strongly with measures of depression as measures of anxiety (Gibbons et al., 2006). The Worry Scale also correlates strongly with measures of state and trait anger, and individual items cover a wide range of coping and emotional responses to dementia. For the NPI and BEHAVE-AD, information about differential relationships with other neuropsychiatric symptoms is not available.

Thus, none of the existing instruments is entirely adequate, particularly as it pertains to convergent and divergent validity, but three instruments (the NPI, BEHAVE-AD and RAID)

have some preliminary support. The NPI or, alternatively, the BEHAVE-AD, can be used to assess neuropsychiatric symptoms in general, including anxiety. For studies where anxiety is a primary focus, the RAID, albeit imperfect, has the best support at this point.

4. Clinical characteristics

In examining the clinical characteristics of anxiety in individuals with dementia, we were guided by three questions. First, what subgroups of individuals with dementia are most likely to present with anxiety symptoms? To answer this question, we specifically examined the roles of demographic characteristics, dementia severity and type, and presence/absence of insight. Second, what is the impact of anxiety on functional outcome and QoL? Third, what are the environmental and social factors associated with greater anxiety in this population?

4.1. Anxiety and demographic characteristics

4.1.1. Sex—Although anxiety symptoms and disorders tend to be more common in women within the non-demented elderly (Stanley & Beck, 2000), most studies using dementia samples did not find sex differences: only two of thirteen studies found greater levels of anxiety among women with AD (Bungener et al., 1996; Ferretti et al., 2001). These two studies, however, used anxiety scales that have not been previously validated in individuals with dementia. Thus, the bulk of the evidence suggests a lack of relationship between sex and anxiety in individuals with dementia (Ballard, Boyle, & Bowler, 1996; Ballard et al., 2000; Hwang et al., 2004; Mendez, McMurtray, Chen, Shapira, Mishkin, & Miller, 2006; Orrell & Bebbington, 1996; Ownby, Harwood, Barker, & Duara, 2000; Paulsen, Ready, Hamilton, Mega, & Cummings, 2001; Porter et al., 2003; Shankar et al., 1999; Teri et al., 1999; Tsang et al., 2003).

4.1.2. Age—Of the nine studies we identified, one found greater anxiety in older patients (Bungener et al., 1996). This study, already cited above, used anxiety scales that have not been validated in dementia. Another study (Ferretti et al., 2001) found greater anxiety in older patients in one sample but not the other; moreover, the association between anxiety and age disappeared after controlling for other variables of interest. The other studies found no relationship between age and anxiety (Ballard et al., 1996; Ballard et al., 2000; Mendez et al., 2006; Orrell & Bebbington, 1996; Paulsen et al., 2001; Shankar et al., 1999; Tsang et al., 2003).

4.1.3. Education—The two studies we identified found no relationship between anxiety and years of education in FTD (Mendez et al., 2006) and AD (Ownby et al., 2000).

4.1.4. Race/ethnicity—Two studies (Chen, Borson, & Scanlan, 2000; Ortiz, Fitten, Cummings, Hwang, & Fonseca, 2006) examined the prevalence of anxiety symptoms in individuals with dementia of different ethnic groups. In one study (Chen et al., 2000), African-Americans with dementia had lower anxiety than Asians and Hispanics with dementia, even after controlling for dementia severity, age, sex, and education. In another study (Ortiz et al., 2006), Hispanics with dementia had higher anxiety than Caucasians with dementia, even after controlling for age, sex and education. In contrast, Hispanics and Caucasians without dementia did not differ in anxiety symptoms. Thus, current data suggest that anxiety may be more prevalent in Hispanics and Asians with dementia than African-Americans and Caucasians with dementia.

4.2. Anxiety and dementia subtype

Six studies (Aarsland, Cummings, & Larsen, 2001; Ballard et al., 2000; Lyketsos et al., 2000; Porter et al., 2003; Skoog, 1993; Sultzer, Levin, Mahler, High, & Cummings, 1993) compared anxiety prevalence in distinct, well-defined types of dementia (see Table 2). In one

study (Skoog, 1993), rates of OCD, phobia, and GAD did not differ between AD and vascular dementia (VaD). Among four studies that examined rates of anxiety symptoms in AD and VaD, two found greater anxiety in VaD (Ballard et al., 2000; Porter et al., 2003), and the other two did not find any significant difference (Lyketsos et al., 2000; Sultzer et al., 1993). In both studies with null findings, anxiety was qualitatively greater in the AD group. Moreover, in one study (Sultzer et al., 1993), sample size was relatively small (N=28 in each group), and in the other study (Lyketsos et al., 2000), rates of anxiety symptoms were unusually low (8% in the AD group and 18% in the VaD group). Thus, anxiety symptoms appear greater in VaD than in AD. Compared to AD, rates of anxiety symptoms may be greater in fronto-temporal dementia (Porter et al., 2003) and similar in dementia associated with Parkinson's disease (Aarsland et al., 2001).

4.3. Anxiety and dementia severity

Five studies examined the relationship between anxiety symptoms and dementia severity (see Table 3). Two studies (Chen et al., 2000;Sclan et al., 1996) found lower anxiety at the profound/terminal stages of dementia, and two others (Lyketsos et al., 2000;Shankar et al., 1999) found no significant effect of dementia severity. The latter two studies, however, did not distinguish between severe and profound/terminal dementia. A fifth study (Forsell & Winblad, 1997) found lower anxiety at the moderate/severe stages. Results of this study are questionable, however, because dementia type was not reported and the instrument used to assess anxiety, the Comprehensive Psychopathological Rating Scale (Asberg, Montgomery, Perris, Schalling, & Sedvall, 1978), has not been validated in dementia. Thus, findings suggest that anxiety is relatively stable across the range of dementia severity, until the profound/terminal stage, where it decreases.

4.4. Anxiety and insight/awareness

Six studies examined the relationship between anxiety and awareness of deficits in individuals with dementia (Ballard et al., 1996; Derouesné et al., 1999; Harwood et al., 2000; Seltzer et al., 1995; Shankar et al., 1999; Verhey, Rozendaal, & Ponds, 1993). The methods used for assessing anxiety and awareness of deficits varied greatly, as did sample characteristics. Some studies assessed awareness of deficits by examining the discrepancy between patient and caregiver ratings of cognitive performance (Derouesné et al., 1999; Seltzer et al., 1995; Verhey et al., 1993), while others asked the caregiver to rate patient insight (Harwood et al., 2000) or based the rating on whether the patient recognized having memory problems (Shankar et al., 1999). Despite these differences, all studies suggested that individuals with retained insight experienced greater anxiety. In some cases, the relationship between anxiety and preserved insight disappeared after controlling for depression (Derouesné et al., 1999; Harwood et al., 2000; Seltzer et al., 1995; Verhey et al., 1993).

4.5. Anxiety, quality of life and functional outcome

In older adults without dementia, anxiety has been associated with reduced QoL, more functional limitations, poorer physical health and reduced activities (de Beurs, Beekman, van Balkom, Deeg, van Dyck, & van Tilburg, 1999; Wetherell, Thorp, Patterson, Golshan, Jeste, & Gatz, 2004). In individuals with dementia, three studies have documented the relationship between anxiety and poorer QoL, with correlations ranging from .30 to .64 (Banerjee et al., 2006; Hoe et al., 2006; Selwood, Thorgrimsen, & Orrell, 2005). In one study (Hoe et al., 2006), the association remained significant after controlling for depression, problem behaviors and dependency. Other variables of interest were not controlled for in the other two studies (Banerjee et al., 2006; Selwood et al., 2005).

Anxiety has been related to other outcomes of interest. In one study (McCurry et al., 2004), anxiety was related to nighttime behavioral disturbances, even though demographic

characteristics, cognitive status and other neuropsychiatric symptoms, including anxiety, were not. These findings are particularly significant as the sample was substantial (N=153), patients were community-dwelling individuals with AD, and the nighttime behavioral disturbances were scored only if they resulted in awakening of the patient's caregiver. In another study, anxiety was related to problem behaviors and limitations in activities of daily living, even after controlling for depression (Teri et al., 1999). Finally, anxiety symptoms have been associated with nursing home placement prospectively, even after controlling for initial cognitive functioning (Gibbons et al., 2002). In this study, a multiple regression revealed that, among five candidate anxiety symptoms, irritability was the sole significant predictor of nursing home placement. Taken together, however, these findings suggest that anxiety is associated with behaviors causing significant concern to caregivers.

4.6. Environmental and social variables

Anxiety has been associated with unmet needs in individuals with dementia living in residential care homes (Hancock, Woods, Challis, & Orrell, 2006). The most common unmet needs in these individuals were lack of daytime activities, psychological distress, lack of company, and memory and communication problems. Anxiety has also been associated with greater dependency, problems in the patient-caregiver relationship and stressful life events (Orrell & Bebbington, 1996). However, the association disappeared after depression was entered as an additional predictor. Overall, there is a paucity of research on the environmental and social variables associated with anxiety, and the existing results do not adequately address the role of depression as a potential confounding or mediating variable.

5. Discussion

The first part of our review focused on conceptual issues: how to define anxiety in this population, how to differentiate symptoms of anxiety from symptoms of dementia, whether anxiety is distinct from agitation and/or depression, and what sources of information should be used when assessing anxiety in individuals with dementia. We found a scarcity of research on these important issues. When designing assessment measures, authors subscribed to underlying assumptions (e.g., by relying solely on information provided by the caregiver) without justifying or discussing them. One exception is a study by Starkstein et al. (2007), who empirically determined which symptoms best distinguish between individuals with dementia with and without a diagnosis of GAD.

More research is needed to address the difficult issue of how to define, conceptualize and operationalize anxiety in dementia. One promising avenue is to examine possible modifications of existing diagnostic categories to address the potential confounds between symptoms of anxiety and symptoms of dementia (e.g., Starkstein et al., 2007). Equally needed is research determining the structure of neuropsychiatric symptoms in dementia, including anxiety. Factor analyses have been conducted, but most used borderline sample sizes (i.e., less than 200 subjects), methods of questionable validity (i.e., orthogonal rotations), and an exploratory rather than confirmatory framework. As a field of study matures and specific models emerge, confirmatory factor analyses provide a more powerful tool for testing and comparing different hypotheses (Tabachnick & Fidell, 1996). At this point, no conceptual framework exists to generate and test specific hypotheses. Whether anxiety and depression belong to the same factor or require distinct factors would be one important hypothesis to be tested. Another important question is the influence of the source of information, i.e., patient, caregiver or clinician. Research on this topic is greatly needed and would help in the development and/or refinement of assessment measures.

Based on our discussion of conceptual issues related to the definition of anxiety in dementia, we devised four criteria that could serve as recommendations for assessment instruments. Our

review of existing instruments showed that all are lacking in important ways. While all instruments attempt to focus on symptoms least likely to be affected by dementia, their approach is based on face validity rather than empirical research. Their psychometric properties are also questionable: while reliability appears acceptable, construct validity has not been demonstrated.

Underlying these limitations is the fact that little attention has been paid to the validity of existing instruments after their original publication. Typically, an instrument is designed, receives initial support for reliability and validity, and is subsequently used by the research and clinical community without further validation. One exception is Gibbons et al. (2006), who found that the RAID correlated as strongly with measures of depression as with other measures of anxiety in individuals with dementia. More studies examining the validity and/or shortcomings of existing instruments are needed to challenge current practices and foster improvement in assessment.

Our review suggests that anxiety symptoms in dementia are associated with QoL and functional outcome, environmental and social variables, preserved insight and greater prevalence of other neuropsychiatric and behavioral symptoms. Much remains to be done regarding the clinical characteristics of anxiety in dementia. There is a paucity of research on the role of environmental variables, social support and social stimulation on anxiety. Excessive noise, lack of privacy and disruptions in routine, for instance, have been associated with greater agitation, aggression and other neuropsychiatric symptoms in individuals with AD living in long-term care facilities (Kunik, Martinez, & Snow, 2003; Zeisel, Silverstein, Hyde, Levkoff, Lawton, & Holmes, 2003). Little is known, however, about the relationship between environmental factors and anxiety specifically, or regarding the role of environmental variables for individuals with dementia who are still living within the community. This lack of research is particularly unfortunate, because such variables could be targets for behavioral or social policy interventions.

The association found in several studies between awareness of cognitive deficits and anxiety in dementia raises interesting possibilities. First, being aware of one's cognitive decline may generate anxiety (Aalten, van Valen, Clare, Kenny, & Verhey, 2005). Second, both awareness of deficits and anxiety may be related to preserved expressive language abilities. Caregivers and clinicians rely heavily on verbal statements for judging awareness of deficits. Similarly, caregivers may rely heavily on verbal reports for judging whether the patient is anxious. Thus, although patients with compromised expressive language may still experience anxiety, they may be unable to verbalize it, and it may remain unnoticed by caregivers. Examining which specific aspects of anxiety (e.g., worry vs. somatic symptoms) correlate most strongly with preserved insight may shed light on this important issue.

Because no randomized-controlled trials have been conducted on the treatment of anxiety in individuals with dementia, we did not include treatment of anxiety in the present review. Existing reviews of pharmacological interventions (e.g., Sink, Holden, & Yaffe, 2005) recommend using anti-depressants, while benzodiazepines are contra-indicated due to their cognitive side effects (Alexopoulos, Jeste, Chung, Carpenter, Ross, & Docherty, 2005). Very little is known about the efficacy of psychosocial interventions. Case studies and uncontrolled studies suggest that increased activities (Qazi, Shankar, & Orrell, 2003), caregiver psychoeducation (Haupt, Karger, & Janner, 2000; Koder, 1998), staff training designed to promote greater empathy and communication (Bråne, Karlsson, & Kihlgren, 1989), and greater involvement of patients in decisions affecting their own care (Bråne et al., 1989) could be effective. Methodologically sound controlled studies are greatly needed to offer patients and their caregivers empirically validated approaches to treatment. Overall, the increased interest in anxiety in dementia over the past decade is timely and encouraging, but more research is

needed to develop better understanding and empirically-based care of anxiety in this population.

A number of limitations should be noted. We did not rate studies according to existing quality guidelines, and instead discussed findings critically on a study-to-study basis. Two representative databases (PubMed and PsycINFO) were reviewed. Searches in other databases could have revealed additional studies, although our systematic checking of cross-references minimizes the risk that we missed critical studies. Studies were included regardless of the method used for assessing anxiety, i.e., continuous measure of anxiety symptomatology, use of a cutoff score on a continuous measure, or DSM-IV diagnostic criteria. A more stringent approach (i.e., mandating the use of diagnostic criteria) would have increased study homogeneity. For most questions of interest, however, no study used diagnostic criteria, and our review would have provided very limited information on the current state of the literature. These limitations notwithstanding, our review provides a comprehensive examination of the existing literature on anxiety in individuals with dementia, and suggests directions for future research.

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Table 1

Factor analyses of neuropsychiatric and behavioral disturbances

Reference	Sample	Anxiety assessment	Rotation	Factors identified
Aalten et al. (2003)	AD (*N*=146), VaD (*N*=32), other dementia (*N*=21), memory clinic	NPI	Orthogonal	Depression/apathy; hyperactivity; psychotic symptoms[a]
Cummings et al. (2006)	AD (*N*=275), memory clinic	NPI	Oblique	Psychotic symptoms; agitation; depression/anxiety; disinhibition; appetite changes
Forsell et al. (1993)	AD (*N*=86), VaD (*N*=32), other dementia (*N*=26), community	CPRS	Orthogonal	Inactivity; depression; anxiety; psychotic symptoms
Frisoni et al. (1999)	AD (*N*=162), AD inpatient unit	NPI	Oblique	Depression/anxiety; psychotic symptoms; disinhibition
Harwood et al. (1998)	AD (*N*=152), memory clinic	BEHAVE-AD	Orthogonal	Anxiety/agitation; psychotic symptoms; aggression; depression; activity disturbance
Mirakhur et al. (2004)	AD (*N*=435), memory clinic	NPI	Orthogonal	Depression/anxiety/agitation; apathy/sleep/appetite; psychotic symptoms; manic symptoms

AD = Alzheimer's Disease; NPI = Neuropsychiatric Inventory; VaD = Vascular dementia; CPRS = Comprehensive Psychopathological Rating Scale; BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease Rating Scale.

[a] Anxiety loaded both on the depression/apathy factor and on the psychotic symptoms factor.

Table 2

Anxiety symptoms and disorders by dementia type

Reference	Sample/source	Anxiety assessment	Criterion	Comparison
Aarsland et al. (2001)	AD (*N*=42), PDD (*N*=42), community	NPI	Positive screening	38% in AD, 31% in PDD**
Ballard et al. (2000)	AD (*N*=92), VaD (*N*=92), hospital dementia care register	Checklist based on DSM-IV	Two or more symptoms	38% in AD, 71% in VaD*
Lyketsos et al. (2000)	AD (*N*=214), VaD (*N*=62), community	NPI	Positive screening	8% in AD, 18% in VaD**
Porter et al. (2003)	AD (*N*=115), VaD (*N*=43), FTD (*N*=33), memory clinic	NPI	Not applicable	Anxiety scores greater in VaD and FTD than in AD*
Skoog (1993)	AD (*N*=64), VaD (*N*=69), community	Clinical interview	Not applicable	AD vs. VaD: - Phobia 1.6% vs. 0%** - OCD, 1.6% vs. 2.9%** - GAD, 18% vs. 23%**
Sultzer et al. (1993)	AD (*N*=28), VaD (*N*=28), neurology clinics	NRS	Not applicable	Anxiety scores greater in AD than in VaD**

AD = Alzheimer's Disease; PDD: Dementia associated with Parkinson's disease; NPI = Neuropsychiatric Inventory; VaD = Vascular dementia; FTD = Fronto-temporal dementia; NRS = Neurobehavioral Rating Scale.

* $p<.05$

** $p>.05$.

Table 3

Relationship between anxiety and dementia severity

Reference	Sample/source	Anxiety assessment	Dementia severity assessment	Results
Chen et al. (2000)	AD (*N*=125), community	BEHAVE-AD	CDR	Less anxiety in profound/terminal dementia *
Forsell and Winblad (1997)	Dementia, unspecified type (*N*=180), community	CPRS	CDR	Less anxiety in moderate/severe dementia *
Lyketsos et al. (2000)	AD (*N*=214), VaD (*N*=62), community	NPI	CDR	No significant relationship with dementia severity
Sclan et al. (1996)	AD (*N*=142), memory clinic	BEHAVE-AD	GDS	Less anxiety in profound/terminal dementia *
Shankar et al. (1999)	AD (*N*=55), VaD (*N*=11), other dementia (*N*=17), inpatients and day hospital	RAID	CDR	No significant relationship with dementia severity

AD = Alzheimer's Disease; BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease Rating Scale; CDR = Clinical dementia rating scale; CPRS = Comprehensive Psychopathological Rating Scale; VaD = Vascular dementia; NPI = Neuropsychiatric Inventory; GDS = Global deterioration scale; RAID = Rating anxiety in Dementia scale.

* $p<.05$.