Assessment and treatment of depression associated with dementia

ABSTRACT

Depression is a frequent diagnosis for people with dementia, with between 25% and 42% of such patients receiving antidepressants. The diagnosis can be challenging to make, and this patient group is more vulnerable to side effects of commonly used medications. This article outlines the diagnostic considerations and therapeutic approaches for managing depression in people with dementia.

Dementia is defined as a progressive decline in cognitive function, with memory being especially affected (Lakhan, 2018) or, more fully as 'a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgement commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour or motivation. Dementia produces an appreciable decline in intellectual functioning, and usually some interference with personal activities of daily living, such as washing, dressing, eating, personal hygiene, excretory and toilet activities' (World Health Organization, 1992). It is usually associated with steady decline in the patient's intellect accompanied by reduced emotional control and a deterioration of social functioning. The acquired cognitive and behavioural impairment will eventually become of sufficient severity that it interferes with social and occupational functioning.

People with dementia can exhibit significant mental state disturbances including confusion, agitation and aggression as part of the pathological processes involved in disease syndromes. These may be provoked or exacerbated by many external factors. Such mental state disturbances are referred to as behavioural and psychological symptoms of dementia (*Table 1*). Work by Robert et al (2005) concluded that behavioural and psychological symptoms of dementia are an almost universal phenomenon with up to 90% of people with dementia being affected.

Table 1. Behavioural and psychological symptoms of dementia

Psychological symptoms	Hallucinations
	Delusions
	Misidentifications
	Depression
	Hypersomnolence
	Anxiety
Behavioural symptoms	Physical aggression
	Wandering or pacing
	Restlessness
	Agitation
	Culturally inappropriate behaviours
	Sexual disinhibition

Depression: common in patients with dementia

Clinical depression is common in patients with dementia (Fava et al, 1997; Henry et al, 2011; Nelson et al, 2011), with the prevalence of case level depression around 15% and milder forms even more common (Wilkinson and Izmeth, 2016). The prevalence of depression is higher in nursing homes, with one American study reporting a rate of 48% (Morley, 2010).

Antidepressant medications are commonly prescribed for people with dementia with between 25% and 42% receiving these drugs (Pitkala et al 2004; Snowdon et al, 2011), although this should be interpreted in the context of a more general increase in antidepressant use for older adults (Guthrie et al, 2010; Hughes et al, 2016). The extent of antidepressant prescription may relate to the possible role that antidepressant medications can have in the development of other forms of neuropsychiatric symptomatology (Henry et al, 2011; Kales et al, 2015).

There are two broad group of patients to be considered. First, there will be those patients who develop depressive symptomatology de novo following or during the course of dementia as a result of the diagnosis. This might be considered a form of reactive depression to what can be a devastating diagnosis, with major implications for an

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CASE STUDY 1: PSEUDODEMENTIA OR PSEUDODEPRESSION?

Nancy, a 75-year-old woman, is in a rehabilitation ward following a recent parietal lobe ischaemic stroke. She has a history of hypertension and osteoporosis. Her family feel that she requires a care home placement, concerned that her cognitive functioning has been declining for at least 6 months before her stroke, to a degree that renders her unable to manage at home. Progress with the rehabilitation team is limited and a Mini-Mental State Examination (MMSE) is significantly reduced at 21/30. While examining her cognitive function, it was noted that she has marked concentration difficulties, noticeable indecisiveness in responding to the questions, with poor motivation and apathy in performing the MMSE. Nancy is commenced on sertraline 50 mg daily as a trial, and 8 weeks later an MMSE is recorded at 27/30. She engages meaningfully with rehabilitation and, following discussions with her family, decides for discharge home with a twice-daily package of care.

Learning points

- Depression may present with cognitive impairment.
- Cerebrovascular disease is associated with the development of depression.

individual's lifestyle (driving, work and planning for the future). Second, there will be patients who have had a diagnosis of depression before their dementia diagnosis who may develop a further relapse of their depression. Earlier-life depression has been shown to be an important risk factor for dementia (Byers and Yaffe, 2011) whereas the nature of the association with later-life depression is unclear. It remains controversial whether depression represents an aetiological risk factor, is part of the dementia prodrome or shares other factors, such as vascular disease, with dementia (Barnes et al, 2012).

Depression is a major reason for patients to be admitted to a nursing home, alongside depressed patients being more likely to be functionally dependent and less likely to engage with rehabilitation programmes (Morley, 2010).

Presentation of depression in people with dementia

The main clinical symptoms of depression are no different for people with dementia and those without (Engedal et al, 2011). Objective and subjective mood is often low, with attendant agitation and increased irritability. There may be associated sleep disturbance, negative or hopeless thoughts, and possible deterioration of cognition. Indeed, the old concept of pseudodementia, depression causing cognitive impairment presenting as a dementia syndrome, still needs to be considered as part of the diagnostic work-up of dementia (Lakhan, 2018). It is essential to involve family members and caregivers to try and obtain an accurate and comprehensive picture of the patient's mental state. Clinicians should always consider other causes for changes in mood including a hypoactive delirium (e.g. infection, electrolyte disturbance, undiagnosed pain, constipation) alongside the impact of prescribed and non-prescribed medications (beta-blockers, calcium-channel blockers, steroids) (Thakur and Blazer, 2008; Engedal et al, 2011). Endocrine and metabolic conditions (hypothyroidism, hypercalcaemia) alongside organic brain disease (stroke, Parkinson's disease) may be associated with the development of depressive syndromes. In *Case study 1* the differential of depression was considered in a patient with post-stroke cognitive symptoms.

In older patients depression can present with physical health symptoms which may provide the basis for physical health investigations (Morley, 2010). Indeed, depression is a major cause of anorexia and weight loss in nursing home residents and older persons in the community (Morley, 2007; Leone et al, 2009). Patients may present with an increase in both nociceptive and neuropathic pain, with depression increasing the perception of pain (Morley, 2008). Depression has been associated with increased falls (Thakur and Blazer 2008), and severe apathy can be confused with or mistaken for a hypoactive delirium in clinical practice unless considered specifically (Radakovic et al, 2015).

Assessment and making a diagnosis of depression

When assessing people with dementia who have a possible diagnosis of depression on the basis of clinical suspicion, it may be helpful to augment a careful history with validated screening tools for this patient group, informing clinical decision making. These tools include the Cornell Scale for Depression in Dementia (Alexopoulos et al, 1988) and the Montgomery and Åsberg Depression Scale (Montgomery and Åsberg, 1979) which have both been reported as being effective in diagnosing depression in patients with dementia (Müller-Thomsen et al, 2005). However, correlation between the scales was better in patients with mild dementia than those with moderate to severe dementia (Müller-Thomsen et al, 2005).

The Cornell Scale for Depression in Dementia (Alexopoulos et al, 1988) is a 19-item scale that measures depression after interviews with the patient and the caregiver. Items are 'mood and related signs', 'behavioural disturbance', 'cyclic function and ideational disturbance' and 'physical signs'. Items are measured on a 3-point scale: 'absent', 'mild or intermittent' and 'severe'. Nine or more points indicate a depressive disorder. The Montgomery and Åsberg Depression Scale (Montgomery and Åsberg, 1979) consists of 10 items, which can be scored from 0 to 6 after an interview. Its use is well established in old age psychiatry studies. The advantage of this scale is that no somatic symptoms are asked about. The authors suggest a cut-off value of 13 points for mild depression.

Although the Geriatric Depression Scale (15-item scoring system useful for when time is short and commonly used in clinics) (Sheik and Yeasavage, 1986) is an accurate screening test for depression in cognitively intact geriatric populations, it does not maintain its validity in populations that contain large numbers of patients with dementia of the Alzheimer type (Burke et

al, 1989). Apathy is defined as a disorder of motivation and is an often-underestimated aspect of many neurodegenerative disorders. It is recognized as a frequent abnormal behaviour in people with dementia but its overlap with depression is poorly understood (Starkstein et al, 2005). It is important that recently developed and validated instruments to detect apathy can be applied in some specific diseases, including Alzheimer's disease (Radakovic et al, 2015), not least because, unlike for depression, there are no established successful therapies (Masud and Pryce, 2018).

Non-drug approaches

When a diagnosis of depression is reached in a setting of dementia, non-drug approaches should be considered. These may range from post-diagnostic support, supporting patients and obtaining social support in the community, to the psychological. National Institute for Health and Care Excellence guidance suggests that for people with mild to moderate dementia who have mild to moderate depression, psychological treatments should be considered instead of antidepressants, unless they are indicated for a pre-existing severe mental health problem (National Institute for Health and Care Excellence, 2018). There is some evidence reported in a Cochrane review that even for patients with so-called mild cognitive impairment, some forms of cognitive behavioural therapy may be of benefit (Orgeta et al, 2014). There has been good evidence that total quality management programmes, or multidisciplinary management (using social worker, family practitioner and mental health nurse) alongside antidepressant treatment, can reduce hospitalizations and referrals (Flaherty et al, 1998; Orgeta et al, 2014).

Patients with progressive cognitive impairment may benefit from a supportive family doctor who is able to listen to concerns, address issues as and when they arise, and promote positive thinking by encouraging good self-care activities. This 'soft' approach may also help family members feel that the implications of a challenging diagnosis are fully understood by their primary health-care provider.

Exercise has emerged as an excellent therapy for dysphoria and possibly even major depression in the nursing home environment (Morley, 2010) alongside broader physical health benefits. However, access to exercise and behavioural therapies may be limited. This is an area that does require a degree of investment and further formal clinical trial data to establish how and where such programmes should be delivered, not least in relation to more atypical presentations of depression in older adults with dementia.

Evidence of antidepressant medications for patients with dementia

Antidepressant medications are less likely to be clinically effective in older adults with dementia but remain an useful option for managing affective disorders (Nelson et al, 2011). The reasons for this reduced efficacy may be related to the underlying pathological processes causing damage to cerebral structures in dementia syndromes, or indeed as a result of a lack of clinical data.

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Orgeta et al (2017) performed a systematic review and meta-analysis to assess the efficacy of antidepressants in patients with Alzheimer's disease. They reported that when assessing response to treatment (six studies, 297 patients treated with antidepressants and 223 with placebo), no statistically significant difference between antidepressants and placebo was found (odds ratio 1.95, 95% confidence interval 0.97–3.92) (Orgeta et al, 2017). The authors noted that despite the importance of depression in this patient group, the limited clinical data mean firm conclusions are hard to draw.

Furthermore, it should be noted that the vast majority of original clinical trials for antidepressant medications did not include older patients or those with a dementia diagnosis, a situation that is not unique to research in the medication sphere (Schilling and Gerhardus, 2017). As a result of the challenges of generalizing trial data to this patient group, there have been several recent studies focusing specifically upon the efficacy of antidepressant medications in dementia.

The Depression in Alzheimer's Disease Study (DIADS-2) of sertraline found it was not associated with any significant improvement in depression within 12 or 24 weeks (Weintraub et al, 2010). Furthermore, the HTA-SADD trial (n=326) comparing mirtazapine and sertraline to placebo for clinically significant depression reported that these agents, given with normal care, are not clinically effective (compared with placebo) for clinically significant depression in Alzheimer's disease (Banerjee et al, 2011). However, the smaller DIADS study (n=44) in 2003 had found that when the potential overlap between symptoms of Alzheimer's disease and depression in Diagnostic and Statistical Manual of Mental Disorders (4th edn) (DSM-IV) criteria was addressed, sertraline was superior to placebo in the Cornell Scale for Depression in Dementia, and the psychiatrists' global impression (Lyketsos et al, 2003).

Looking more broadly at the trial evidence to date, although most patients recruited into clinical trials investigating the efficacy of selective serotonin-reuptake inhibitors or serotonin–norepinephrine reuptake inhibitor in dementia had improved depressive symptoms compared to baseline, the improvement in the placebo group was also marked. Furthermore, although several reviews have reported that, in general, antidepressant medications are well tolerated, with withdrawal rates from clinical trials secondary to adverse reactions similar to those of placebo,

CASE STUDY 2: THE RISK OF SIDE EFFECTS

John is a 71-year-old recently retired accountant with newly diagnosed Alzheimer's dementia at memory clinic, osteoarthritis of the hip and hypertension. Current medications are lisinopril 10 mg and amlodipine 10 mg. John, waiting to see the post-dementia support service for discussion about acetylcholinesterase inhibitor ('anticholinesterase') therapy, visits his family doctor, distraught about his diagnosis. He is not sleeping and feels a burden to his family although he denies suicidal thoughts. His doctor starts sertraline 50 mg and plans a review in 6–8 weeks.

Unfortunately John is admitted to his local hospital 3 weeks afterwards with an upper gastrointestinal bleed. He had been taking over the counter ibuprofen for his sore hip alongside his antidepressant. He informs the admitting doctor he has not been eating much as he felt sick on the new tablets so has just been taking ibuprofen with water. He is discharged from hospital and will have his medication reviewed following his clinic appointment with the post-dementia support service.

Learning points

- Adverse drug reactions associated with antidepressants are more common in older adults. This should be highlighted when the medication started.
- Patients should be advised to avoid concomitant non-steroidal medications when starting selective serotonin-reuptake inhibitors initially. Gastric protection may be justified in at-risk individuals.

the experience of side effects from trials and in clinical practice vary greatly (Hieronymus et al, 2018). Older antidepressant medications such as tricyclic antidepressants have been reported to be associated with benefits above those of placebo (Petracca et al, 1996) although larger studies were unable to replicate these findings (Reifler et al, 1989). Where tricyclic antidepressants and selective serotonin-reuptake inhibitors have been directly compared, similar efficacy has been reported (Wiese, 2011). However, the side-effect profile of older agents may limit their use in older people with dementia.

Starting antidepressant medications

Following clinical assessment, if a decision to commence therapy is made an selective serotonin-reuptake inhibitor generally would be first line, with mirtazapine considered if insomnia was a problematic aspect of the clinical presentation (Engedal et al, 2011). Of this drug group fluoxetine is generally best avoided given its long half-life and prolonged side effects, with paroxetine not recommended as first line as it has the largest anticholinergic burden of the selective serotonin-reuptake inhibitors and short half-life making the medication difficult to withdraw. Citalopram or escitalopram may be effective in the presence of an electrocardiogram with normal QTc interval, but their interactions with other medications and QTc considerations mean that they may be difficult to use in practice. However, for otherwise physically robust elderly patients these may be a good option.

In general an age-appropriate dose should be prescribed for a minimum of 6 weeks before adjudging the medication to be ineffective. If there has been a partial response, it may be sensible to trial for another 6 weeks. If there has been a response to the prescribed medication, then the medication should be continued for at least 6 months. A Cochrane review suggested that continuing antidepressant medication for 12 months appeared to be helpful with no increase in harm although this was based on three small studies (Wilkinson and Izmeth, 2016). The DESP study (Bergh et al, 2012) reported that discontinuation of antidepressant medication in patients with dementia led to an increase in depressive symptoms after 25 weeks of treatment cessation compared to those who continued treatment. Indeed, a randomized controlled trial of maintenance treatment in older adults, many of whom had first episode depression, found continuing with antidepressant medication was beneficial over 2 years (Reynolds et al, 2006).

Patients should be counselled about common adverse drug reactions, with *Case study 2* illustrating a not uncommon issue in clinical practice. Patients should be aware of gastric side effects, and the risk of interaction with other commonly used medications.

It is advisable to review patients after 6 weeks of starting treatment to review clinical response, and to consider whether the dose can be increased. The highest tolerated dose should be prescribed, as it is not appropriate to continue an ineffective low dose of an antidepressant drug. Referral to old age psychiatry should be considered if there is diagnostic difficulty, high risk of suicide or self harm, little or no response to two first-line antidepressant agents, or self neglect.

Challenges of antidepressant prescription

Unfortunately, depression commonly complicates the clinical picture in dementia and the therapeutic approaches can be limited. In clinical practice it can be very challenging to manage depression in this patient group. This article has included three clinical cases which illustrate some of the challenges around using antidepressant medications, including the potential for side effects, particularly when used in combination with other agents, and the fact that the advancing dementia process may cause challenging symptoms to address with medical therapy.

Case study 3 provides an example of one of the most challenging aspects of this area, the expectation of a prescription by family or nursing home staff. The limited evidence base should be touched upon with patients and their care-givers so as not to provide unrealistic expectations. Open communication with family members may also prevent the continuation of a prescription of antidepressants in the event of poor response.

Conclusions

Depressive symptoms are a common comorbid psychiatric presentation for patients with dementia syndromes. Unfortunately, the evidence base for antidepressant medications in people with dementia is limited. In addition, with patients generally being frail and multi-morbid this group may be more susceptible to the side effects of antidepressants leading to iatrogenic admissions and health-care contacts. The limited effect of antidepressant

medications may well relate to the underlying dementia processes, alongside the well-recognized limitations of drug therapy for depression given its complex pathophysiology.

Therefore, based upon current evidence clinicians should be cautious and considered when commencing antidepressant medications, evaluating potential availability and suitability of non-drug approaches. Where pharmacotherapy is indicated, response to treatment should be closely monitored and patients who are not responding either taken off treatment or trialled on another agent based upon clinical judgement. Without this considered and judicious approach there is a risk that by allowing our desire to help people with dementia to overcome the available evidence, we may inadvertently cause our patients harm. **BJHM**

Conflict of interest: none.

KEY POINTS

- Case level clinical depression in patients with a diagnosis of dementia is around 15%. Clinicians should consider organic diagnoses, such as delirium, as a differential in patients where diagnosis is being made.
- The Cornell Scale for Depression in Dementia and the Montgomery and Åsberg Depression Scale have been well validated for patients with mild dementia, with less efficacy for moderate to severe dementia.
- Non-drug approaches have benefits for the right patients – psychological therapies, post-dementia diagnostic support and broader social prescribing may all be considered.
- Any prescribed antidepressant medication should be started at the lowest dose considering the patient's comorbid health conditions, and reviewed within 6–8 weeks.
- The current evidence base for antidepressant medications in patients with dementia and depression is limited, although the data report that selective serotonin-reuptake inhibitors are generally well tolerated with low trial withdrawal rates secondary to side effects.

CASE STUDY 3: POOR RESPONSE OR DETERIORATING DISEASE?

Lucy is an 80-year-old nursing home resident with advanced Alzheimer's dementia alongside chronic obstructive pulmonary disease, hypertension, angina, dyslipidaemia and type 2 diabetes. Following a clinician-led review rationalising her medications she is on the following current regimen: donepezil 10 mg daily, simvastatin 20 mg daily, metformin 500 mg twice daily, nitroglycerin spray and salbutamol as required. Her GP started sertraline 50 mg 3 months ago as the nursing home staff said Lucy had become withdrawn and apathetic. Lucy normally chatted away (incoherently) and engaged with her family. Her doctor excluded infection and baseline bloods and urine were unremarkable. The home get back in touch and request a different antidepressant. The nursing sister reports that they and her family are still concerned that she is eating poorly, losing weight and does not want to leave her room.

Learning points

- Open communication with family members about the challenges of treating depression alongside a progressive dementia may help in such challenging cases.
- Regular review of antidepressants in this group of patients is important. The dose should have been reviewed at 6 weeks.

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