Treatment for depression comorbid with dementia

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ABSTRACT

Depression is a common comorbidity in dementia. Randomised controlled studies of antidepressants do not show a significant improvement in depressive symptoms in patients with comorbid dementia and are known to lead to an increase in side effects. However, there are relatively few studies of depression in dementia, and drawing firm conclusions about the use of antidepressants is limited by the amount of data available. Furthermore, it is unclear whether data can be extrapolated from similar populations (eg, those with late-life depression) to inform pharmacotherapy in this patient group. Given the lack of effectiveness and risk of side effects associated with pharmacological treatments, psychological interventions may offer important therapeutic benefits. There is evidence for the effectiveness of individual psychological therapy, and further research will establish which psychological approach is the most effective. Some studies have shown an improvement in depressive symptoms using structured sleep hygiene programmes, exercise, arts interventions and music therapy. These studies are hampered by small data sets, and the benefits to individuals may not be well captured by standard outcome measures. At present, the best evidence for arts-based approaches is in music therapy. Depression with comorbid dementia responds well to electroconvulsive therapy and this is a useful treatment modality for those with severe or life-threatening depressive symptoms. Alternative neurostimulation techniques such as transcranial magnetic stimulation are not widely used at present and further research is needed before they can be a more widely used treatment modality.

INTRODUCTION

In the UK, approximately 850 000 people are living with dementia and this number is predicted to rise to over two million by 2051.[1] Dementia is defined 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".[2] As the condition progresses, the person may also experience changes in their emotions and behaviour. Dementia can be divided into subtypes based on differing clusters of symptoms and pathophysiology.

Depression is common in older adults, affecting up to 9.3% of over 60s.[3] Either Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition or International Statistical Classification of Diseases and Related Health Problems, 10th Revision criteria can be used for diagnosis, and both require the presence of one or two core symptoms for most of each day for 2 weeks, including low mood, anhedonia and/or anergia.[2 4] These criteria help to distinguish between symptoms of depressive disorder and apathy (in which the core features of low mood and sadness are present). The presence of additional cognitive and somatic symptoms define the severity of depression. It is important to remember that older adults report more somatic symptoms and may not initially present with low mood.[5]

The prevalence of depression is higher in individuals with dementia, ranging from 20% in Alzheimer's disease to 37% in frontotemporal dementia.[6] Memory problems and differences in presentation mean that diagnosing depression in those with dementia can be challenging. The Cornell Scale for Depression in Dementia[7] was developed and validated specifically to address these difficulties and is administered by a clinician using information provided by the patient and a caregiver. This article will review the research covering a range of biopsychosocial interventions to manage depression in adults with dementia.

METHODS

The pertinent literature was identified using PubMed, Google Scholar and Cochrane Databases between 1985 and July 2019 using the terms "dementia and depression" plus "medication" or "antidepressant" or "antipsychotic" or "hypnotic" or "benzodiazepine" or "dual therapy or "augmentation" or "ECT" or "Electroconvulsive therapy" or "TMS" or "Transcranial Magnetic Stimulation" or "tDCS" or "transcranial Direct Current Stimulation" or "Magnetic Seizure Therapy" or "vagus nerve stimulation" or "deep brain stimulation". Additionally, the electronic databases AMED (allied and complementary medicine) (1985–2019), Embase (1980–2019) and Medline (1946–2019) were searched for the terms "Dementia" OR "Alzheimer's Disease" AND "depression". To search for psychological interventions, the terms used were: "psychotherapy" OR "counselling" OR "cognitive therapy" OR "psychological intervention"; "family therapy" OR "couples therapy"; "group therapy" OR "support group". To search for social interventions, terms used were: "sleep hygiene", "light therapy"; "exercise"; "education" OR "psychoeducation"; "art therapy"; "dance therapy"; "music therapy". Reference lists and citing articles of identified articles were also examined. The main findings are reported in table 1.

Pharmacological interventions

Monotherapy

The latest National Institute for Health and Care Excellence (NICE) guidelines on dementia do not recommend antidepressants for new-onset mild to moderate depression in those with mild to moderate

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Table 1 Main findings in the treatment of depression comorbid with dementia

Intervention		Main findings
Pharmacological	Monotherapy	Antidepressants are not recommended for new-onset mild to moderate depression in those with dementia.
	Dual therapy and augmentation	Limited research evidence is available; some clinicians provide anecdotal evidence to support this strategy.
	Monitoring of physical health	With SSRIs, pay attention to the risks of hyponatraemia and GI bleeding.
Psychological	Individual therapy	There is some evidence for the effectiveness of cognitive–behavioural therapy and problem adaptation therapy.
	Couple and family therapy	There is little evidence for the efficacy of family and couples therapy.
	Group therapy	Some evidence for the effectiveness of group therapy, but substantial heterogeneity between studies.
Social	Sleep hygiene	Overall evidence does not support a significant treatment effect using sleep hygiene approaches.
	Exercise	Overall evidence does not support a significant positive impact of exercise on depressive symptoms.
	Patient and carer education	Relatively little work in this area and insufficient evidence to suggest patient and carer education is effective in reducing depressive symptoms.
	Arts and museum attendance	Music therapy has the best evidence and further work is needed to establish the benefits of other modalities.
Neurostimulation	ECT	Severe depression with comorbid dementia responds well to ECT and provides rapid resolution of symptoms.
	TMS	Limited literature on efficacy of TMS for treating and further studies are needed to evaluate its efficacy.

ECT, electroconvulsive therapy; GI, gastrointestinal; SSRIs, selective serotonin reuptake inhibitors; TMS, transcranial magnetic stimulation.

dementia.[8] The evidence for antidepressant monotherapy to treat comorbid depression in dementia has been reviewed by the Cochrane database.[9] The authors found that high-quality randomised controlled trials (RCTs) of antidepressants did not affect scores on depression rating scales, cognitive function or activities of daily living. Furthermore, patients on an antidepressant were more likely to experience side effects or drop out of trials. There was moderate quality evidence suggesting that more patients taking an antidepressant (40%) were likely to recover at 6 to 12 weeks than those taking a placebo (21.7%). The trials included both older and newer antidepressants, but there were not enough data available to estimate the efficacy of individual medications. A post hoc exploratory analysis[10] of the large multicentre Health Technology Assessment Study of the Use of Antidepressants for Depression in Dementia (HTA-SADD) trial in the UK suggested that mirtazapine may be effective in a subgroup of patients with dementia with more prominent mood and psychological symptoms; however, the authors were careful to note this finding should not change clinical practice due to lack of power. No further trials of antidepressant monotherapy have been published or registered.

Dual therapy and augmentation

Many patients with dementia will also be prescribed an anxiolytic or hypnotic in addition to an antidepressant[11]; however these are for other behavioural and psychological symptoms rather than for depression. Trials of dual therapy or augmentation (antidepressant plus another medication) in late-life depression exclude patients with dementia; therefore, no research evidence exists in this group. However, some individual clinicians have developed their own recommendations based on anecdotal evidence or extrapolations from successful results obtained in patients with late-life depression without cognitive impairment.[12] A large pragmatic clinical trial (Optimizing Outcomes of Treatment-Resistant Depression in Older Adults [OPTIMUM]) is currently investigating the efficacy and safety of switching and augmentation strategies in older adults with treatment-resistant late-life depression and these results, when published, may inform our treatment of patients with comorbid dementia.[13]

Monitoring of physical health and side effects

When commencing antidepressants in older people, the NICE recommends that clinicians consider the impact of age, physical health and other medications.[14] Selective serotonin reuptake inhibitors (SSRIs) are considered first line due to their tolerability. Since citalopram is known to increase the risk of QTc prolongation in older adults, sertraline is often preferred. However, SSRIs are associated with an increased risk of intracranial haemorrhage and gastrointestinal bleeding, therefore co-prescription of a gastroprotective medication should be considered. SSRIs are associated with hyponatraemia, and older patients are especially at risk. The Maudsley Prescribing guidelines recommends that patients at high risk should have serum sodium measured at baseline, 2 and 4 weeks and then 3 monthly.[15] Mild hyponatraemia (>125 mmol/L) can be managed with fluid restriction and daily sodium levels; however, severe hyponatraemia (<125 mmol/L) can life-threatening and the patient should be admitted to acute hospital for treatment and the drug immediately discontinued. There is also an increased risk of postural hypotension and falls, and an individual risk–benefit analysis should be undertaken.

Psychological interventions

Given the lack of effectiveness and risk of side effects associated with pharmacological treatments,[9] psychological interventions are an important potential line of treatment for depression in dementia. The recent NICE guidelines recommend that this is considered for people with mild to moderate dementia who have mild to moderate depression.[8] A number of reviews, including a Cochrane review,[16–18] concluded there is evidence that psychological treatments can reduce symptoms of depression in dementia, but also commented on the heterogeneity of the literature; others highlighted the need to further establish the efficacy of psychological interventions.[19]

Individual therapy

Cognitive–behavioural therapy (CBT) involves challenging negative cognitions, developing coping skills and increasing pleasurable activities. The evidence for individual CBT is mixed with some studies showing a significant improvement in depressive symptoms[20] and others showing no improvement.[21] Evidence for other types of psychotherapy is mixed, one RCT showed that interpersonal therapy increased time to remission in people with dementia[22] but other RCTs have shown no effect of psychotherapy.[23] Problem adaptation therapy combines problem solving and behavioural therapy and has also been shown to reduce symptom severity and increase remission in depression in mild dementia.[24] In summary, there is evidence for the effectiveness of individual psychological therapy in patients with depression

in dementia. Further work is needed to establish which psychological approach is the most effective.

Couple and family therapy

In contrast to individual psychological approaches, there are few studies on the effectiveness of family and couple therapy in addressing depression in dementia, and the majority of studies focus on carer outcomes.[25] A number of papers mentioned in the section on individual approaches involve elements of working with carer–patient dyads to reduce depressive symptoms in patients, although these approaches do not follow a specific model of systemic family therapy.[20 24] There is little evidence for a change in depressive symptoms in patients following family interventions.[26] Overall there is little evidence for the efficacy of family and couples therapy in addressing depression in people with dementia.

Group therapy

There are a variety of studies looking at the effectiveness of group therapy in reducing depressive symptoms, both in the early stages of dementia and also in nursing home settings. Evidence for group psychotherapy in the early stages after diagnosis with dementia is mixed.[18] A recent trial using CBT techniques within nursing home-based group therapy showed a significant reduction in depressive symptoms.[27] In summary, there is evidence for the effectiveness of group therapy in dementia, but, as with individual therapy, the literature is very heterogeneous and further work is needed in this area.[19]

Social interventions

Sleep hygiene

Sleep hygiene includes wakefulness and natural light exposure during the day, avoiding caffeine and alcohol, having a bedtime routine and sleeping in a quiet dark environment at night. The most researched aspect of sleep hygiene in people with dementia is the effect of bright light therapy (BLT).[28] In older adults with dementia, sleep–wake patterns may be disturbed because there is less exposure to light due to institutionalisation, reduced outdoor activity and sensory impairment. In addition, degenerative changes in the suprachiasmatic nucleus of the hypothalamus may result in reduced regulation of circadian rhythms.[28] Hickman *et al* found BLT led to a reduction in depressive symptoms in women but an increase in men, and overall did not support BLT as a treatment for depression in dementia.[29] Other studies have shown BLT reduces depression,[30] but this is not consistently replicated and at present there is no sufficient evidence to suggest that BLT is effective,[28] even when combined with other interventions such as exercise and BLT.[31] In summary, while some studies have shown an improvement in depressive symptoms, overall evidence does not support a significant effect of sleep hygiene, including BLT, on depression in dementia.

Exercise

Exercise may impact on cognition generally by improving cerebral perfusion and on depression specifically by altering endorphin pathways and monoamine levels.[32] In addition, exercise has the potential to improve function and activities of daily living, boosting self-esteem and self-efficacy. There is evidence from nursing home-based studies for a reduction in depression when residents engaged in exercise.[33] Other studies are less promising and fail to show a significant impact on depressive symptoms in nursing home-based trials[34] and community settings,[35] using a range of exercise interventions. A number of reviews give an overview of exercise in depression in dementia, some of which suggest exercise is beneficial in reducing depressed mood.[36] However, the majority of reviews conclude there is no significant effect of exercise,[19] including a recent Cochrane review.[32] In summary, although some trials have shown a positive impact of exercise, at present the evidence does not show a convincing effect of exercise on depressive symptoms in people with dementia.

Patient and carer education

Patient and carer education encompasses a wide range of types of information such as information about the nature of dementia and its progression, treatments available and local support services. Education can be provided in individual or group settings and different information is relevant at different stages of dementia. NICE[10] recommends providing relevant information to people with dementia and their carers. There is relatively little evidence on how education for patients and carers may impact on depressive symptoms in dementia. A review looking at the impact of carer interventions in dementia found depression tended to be reduced by carer education.[37] However, there has been relatively little work in this area and currently there is insufficient evidence to suggest patient and carer education is effective in reducing depressive symptoms in dementia.

Arts and museum attendance

Art therapies are widely used for people with dementia and include a number of modalities, such as music, dance, visual art and gallery or museum visits.[38] The arts may be beneficial by offering a means of self-expression, communication and enjoyment to improve well-being, and these modalities remain accessible even in advanced stages of dementia.[39] In a systematic review of creative arts therapies including music, dance and visual art, there was a reduction in the emotional symptoms of dementia. However, there is a lack of systematically designed studies, and the benefits of engaging in arts-based therapies may not be well captured by studies focused mainly on outcomes.[38]

Few RCTs look at dance therapy in dementia and no existing trials met criteria for inclusion in a recent Cochrane review[40]; however, qualitative studies show it to be enjoyable and empowering for participants.[41] Music therapy is a more promising area, with two recent reviews showing evidence that in the care home setting music therapy reduced depressive symptoms in dementia[42] and that music may be one of the most effective non-pharmacological treatments for emotional disorders.[17] It appears then that although further work is needed, especially in community settings, there is evidence for music therapy for depression in dementia.

Few RCTs have been carried out looking at the impact of visual arts on mood in dementia, and a recent Cochrane review found insufficient evidence to draw conclusions about the effectiveness of art therapy in dementia.[43] Some evidence suggests that visits to museums and galleries promote improvements in mood.[44] However, given the relative lack of evidence, it is not possible to comment on whether museum and gallery attendance reduces depressive symptoms in dementia. In summary, the best evidence for arts reducing depressive symptoms in dementia is for music therapy, and further work is needed to establish the benefits of other modalities.

Neurostimulation

Neurostimulation has been used effectively in depressive disorder and in some other neuropsychiatric diseases. The largest

evidence base relates to electroconvulsive therapy (ECT), though there is a rapidly developing literature base for other techniques including: transcranial magnetic stimulation (TMS), transcranial direct current stimulation, magnetic seizure therapy, vagus nerve stimulation and deep brain stimulation. There is a more limited literature pertinent to treatment of depression in dementia, and good quality studies focus on the techniques of ECT and TMS, although using small sample sizes.

Electroconvulsive therapy

Depression with comorbid dementia responds well to ECT. This is in line with compelling evidence from existing studies on depression, which show that ECT has rapid antidepressant action in patients with severe and refractory depression. Studies of ECT for depression in patients with dementia are small. Oudman *et al* studied 19 patients with depression and dementia who underwent ECT.[45] Of these, 13 (68%) reported improvement in depressive symptoms, with 9 (47%) showing partial or complete remission. Side effects including a decline in general cognition, orientation or memory affected six (31%) patients, but most recovered over a 2-month period.[46] Takahashi *et al* followed eight patients with Lewy body dementia and comorbid mood symptoms, who were given six sessions of ECT.[45] All reported significant improvement in mood symptoms with minimal side effects, suggesting that ECT can be used to alleviate low mood in patients with Lewy body dementia.

In patients with dementia, the advantage of ECT is its potential for rapid resolution of symptoms, and the possibility of avoiding some of the drug-related side effects of antidepressant and antipsychotic medication. Studies have supported the safety and efficacy of ECT in older adults, including patients over 75 years old with dementia and multiple medical comorbidities.[46] The main side effect is a relatively higher risk of adverse effects on cognition.[46] ECT administered that using the right unilateral method has fewer cognitive side effects compared with bilateral ECT, with similar efficacy, so this is preferable in patients with depression and comorbid dementia.[47]

Transcranial magnetic stimulation

TMS is a non-invasive technique, which does not need an anaesthetic. It uses a coiled wire encased in plastic above the scalp, with a rapidly changing current to generate an electric current in specific brain areas. It has growing evidence for use in the treatment of depression,[48] but a more limited literature on efficacy of its antidepressant action in patients with dementia. Out of the five studies which applied repetitive TMS (rTMS) to patients with Alzheimer's dementia, three excluded depression as a comorbidity, and others focus on the potential for TMS to ameliorate cognitive deficits in dementia, rather than to improve mood.[49] Ren *et al* did not exclude patients with depression, and the authors reported an improvement in depressive symptoms after TMS treatment, measured using the Geriatric Depression Scale.[50] This improvement in depressive symptoms may be a result of enhanced cognitive performance after treatment with rTMS.

As an alternative to ECT, rTMS appears to be superior to ECT in terms of cognitive side-effects, and is associated with fewer adverse effects on cognition. However, more studies, with larger patient groups are needed to evaluate its efficacy, before it can be included in the routine management of depression in patients of dementia.

CONCLUSIONS

There is a disappointing lack of evidence for effective treatment of depressive symptoms and depressive disorder in those with dementia. It remains unclear if extrapolating data from similar populations are relevant to this patient group, but in the absence of better options clinicians may find themselves relying on available research into late-life depression. ECT remains an effective treatment, but only in those with severe or life-threatening disease. There has been much work exploring non-pharmacological approaches to treatment, with some positive findings that may have real benefits for individuals and their caregivers in terms of symptom reduction and increase in well-being. There is increasing awareness about the needs of patients with depression and dementia, and together with work done so far, this should be a stimulus for further research to investigate pharmacological and non-pharmacological treatments, including important ethical considerations.[51]

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