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Treatments for Depression in Older Persons with Dementia

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DEPRESSION IN DEMENTIA

Dementia itself is not a disease, but a constellation of symptoms caused by diseases and disorders that affect the brain, including Alzheimer's disease (AD), Parkinson's disease (PD), diffuse Lewy body disease (DLBD), strokes, and others. Dementia involves progressive loss of memory and other cognitive functions such as problem-solving and emotional control. The earliest diagnosable stage of dementia is referred to as mild cognitive impairment (MCI). Although MCI does not always lead to dementia, for those who do develop dementia, abilities to independently perform instrumental and basic activities of daily living are generally impaired as the condition progresses.

Behavioral and psychological symptoms of dementia (BPSD), also frequently referred to as neuropsychiatric symptoms of dementia, affect up to 95% of those with dementia during the course of the illness [1]. Symptoms of depression are especially common in mild cognitive impairment and throughout the course of dementia. Reported prevalence of depression or depressive symptoms in persons with dementia ranges from 0 to 96% [2–5], while moderate to high rates of depression or its symptoms are consistently reported for persons with MCI (i.e., 36% by Palmer and colleagues[6]; 63.3% by Sofrizzi and colleagues[7]; 39% by Hwang and colleagues[8]). The wide range of prevalence for depression in dementia is due to several factors, including differences in researchers' focus on symptoms versus specifically defined depressive disorders, diverse study samples varying in causes of dementia, stage of illness, country of residence, and placement of patient, and variation in the instruments used to assess depressive symptoms and disorders.

OUTCOMES OF DEPRESSION IN DEMENTIA

The occurrence of depression occurring in people with MCI or dementia can lead to a number of negative outcomes. For example, pre-existing depression has been identified as a predictor of, or risk factors for, subsequent dementia. One meta-analysis[9] estimated that persons experiencing depression have approximately double the risk of developing dementia than those without a prior history of depression, and more recent study findings concur [6, 10]. Depression may also be a risk factor for progression from MCI to dementia. Several studies report an association between baseline depressive symptoms in participants with MCI and later progression to dementia [11–15].

Comorbidity of cognitive impairment and depression has been associated with increased mortality[16] reduced quality of life [17–20] and increases in caregiver burden and distress [17, 21, 22]. Possibly due to the negative impact on caregivers, co-morbid depression and cognitive impairment are associated with higher rates of institutionalization of the demented care recipient [23–25].

PHARMACOLOGICAL TREATMENT OF DEPRESSION IN DEMENTIA

Both pharmacologic and nonpharmacologic treatment approaches have been found to be helpful in reducing depression in cognitive impairment and dementia. Pharmacological treatment of depression in patients with dementia, although common, presents some unusual difficulties. Patients with dementia have more comorbid illnesses than non-demented peers, with approximately 60% of those with AD having 3 or more medical conditions. This heightened level of comorbidity results in the use of multiple medications. Therefore, drug interactions and polypharmacy may help provoke BPSD in some patients with dementia, or may play a part in driving these patients' sometimes atypical responses to the drugs used to treat BPSD[26]. Given their physical and cognitive frailty, persons with dementia may also be particularly susceptible to adverse effects. Since dementia patients may be less able to communicate, clinicians and caretakers must carefully observe patent's behavior for evidence of adverse events when new medications are introduced. Prescription of new medications intended to treat depression or other BPSD in dementia patients should always be made using the familiar adage originated for dosing the elderly, "Start low and go slow" [27].

Antidepressants

Antidepressants are frequently prescribed for treatment of depression in dementia. A recent meta-analysis [27] covered treatment of depression with tricylic antidepressants (TCA; imipramine and clomipramine), and selective serotonin reuptake inhibitors (SSRI; sertraline and fluoxetine) in five studies on patients with dementia. Treatment response and remission was superior to placebo in the combined sample, but significant declines in cognitive scores occurred during the use of TCAs in both studies employing them. Reviews of research on the pharmacological treatment of BPSD in general [28–30] indicate positive effects of various antidepressants (including sertraline, fluoxetine, citalopram, trazodone, and moclobemide) on depression in dementia, with citalopram and sertraline being the most commonly prescribed [31–33]. Case reports and small pilot studies indicate that other antidepressants, including trazadone, buspirone, and mirtazapine, may improve depression in patients with dementia, but no large trials have been performed in persons with dementia to date [28, 29, 34]. The practice guidelines recently issues by the Work Group on Alzheimer's Disease and Other Dementias of the American Psychiatric Association [35] currently support SSRIs as the first pharmacological treatment of choice for depression in dementia, as SSRIs tend to be better tolerated than other antidepressants. However, the Work Group suggests that if patients with dementia cannot tolerate higher dosages when needed for remission of depression, trials of alternative antidepressants such as bupropion, venlafaxine, and mirtazapine may be considered.

Anticholinergics

Newer medications that show potential promise in the treatment of depression in dementia include anticholinergics, anticonvulsants, and memantine. Decreased cholinergic activity, primarily resulting from decreased acetylcholine concentrations caused by dementia-related neurological changes, has been associated with decreased cognitive ability in dementia, as well as increases in BPSD, including anxiety and depression [36]. Cholinesterase inhibitors have been used to successfully target these problems by increasing levels of acetylcholine in

patients with mild to moderate dementia [37]. In particular, a recent randomized controlled trial demonstrated improvement in depression scores of patients with dementia, as measured on the Hamilton Depression Scale, for patients given rivastigmine or a combined regimen of rivastigmine and fluoxetine, compared to placebo [38].

Anticonvulsants

Anticonvulsants, through their modulation of GABA, may be another class of agents for treating BPSD. GABA concentrations are often decreased in cortical regions of the brain of patients with dementia, and medications that increase GABA levels have been shown to improve mood disorders [28]. However, trials of the anticonvulsant carbamazepine to treat BPSD have yielded contradictory results [39], or have not reported data on depression. At least one clinical trial of valproate, another anticonvulsant, resulted in significant improvement in melancholic, sorrowful and anxious behaviors[40], but the results of other small trials of valproate are contradictory[30]. Preliminary trials of the anticonvulsant lamotrigine in elderly patients with dementia also noted improvement symptoms of agitation and depression[41].

Memantine

Memantine, a drug that reduces excessive glutamate receptor signaling, has also been studied in patients with dementia. Glutamate signaling is important for learning and memory, but in some patients with dementia it may increase to “oversignalling” levels that destroy neurons. A recent review and meta-analysis of the research on memantine for the treatment of psychological symptoms of dementia showed small but significant improvements on the Neuropsychiatric Inventory, with limited adverse effects[42].

In summary, a variety of pharmacological treatments have some efficacy in the treatment of depression in dementia, but care must be exercised in their use with this population of generally frail older persons to avoid adverse effects. Alexopoulous and colleagues constructed an expert consensus response after surveying 50 experts in dementia from North America on preferred, alternate, and unacceptable treatment choices for BPSD[43]. The general consensus was that SSRIs were the preferred pharmacological treatment for depression in patients with dementia. Further research appears to be needed to establish the effects of both older and newer pharmacological options on depression in dementia patients.

NON-PHARMACOLOGICAL TREATMENTS FOR DEPRESSION IN DEMENTIA

Clinical guidelines specify the use of non-pharmacological treatments for BPSD before pharmacological treatments are tried [28, 44]. Nonpharmacological therapies that specifically target depression or its symptoms fall roughly into three categories: emotion-oriented therapies, brief psychotherapies, and sensory stimulation therapies.

Emotion-Oriented Therapies

The primary aim of emotion-oriented therapies is to fit the therapy to emotional needs of people with dementia, and by doing so, improve their quality of life, social functioning, and ability to cope with the cognitive, emotional and social consequences of the disease as they subjectively experience them [45]. Examples of emotion-oriented approaches include reminiscence, reality, validation, and simulated presence therapy.

Reminiscence therapy encourages persons with dementia to talk about their pasts, generally using memory aids such as old family photos and personal objects [46]. Reality orientation therapy is based on the theory that inability to orient themselves reduces the ability of those with dementia to function, and that confusion can be reduced by giving repeated orientation

clues, such as the time of day, date, season, or names. Validation therapy assumes that the person with dementia may choose to retreat to an inner reality based on emotions, rather than trying to wrestle with failing intellectual powers. The therapist accepts the resulting disorientation of a person with dementia and validates his or her presumed feelings, providing a background for meaningful conversations addressing their emotions [47]. Simulated presence therapy involves exposing an individual with dementia to audio or videotaped recordings of loved ones [48].

Unfortunately, the limited literature available on emotion-oriented therapies in patients with dementia includes few studies with depression as a measured outcome. Even when these outcomes are reported, findings on the effects of emotion-oriented therapies on these and other BPSD are inconsistent and based on limited or methodologically questionable studies[49–55]. Despite several positive clinical reports of efficacy for these interventions, there is currently insufficient evidence for their effectiveness in reducing any BPSD, and almost no research providing data on their effects on depression. However, numerous anecdotal and research reports of clinical effectiveness, and the client-centered nature of these individualized therapies, suggest that they might yet prove to be of value. More methodologically sound, larger, and well-controlled randomized trials are urged by their supporters (e.g., Finnema and colleagues[45]).

Brief Psychotherapies

Brief psychotherapies that have been used with some success in persons with depression in dementia include behavior therapy and cognitive-behavioral therapies. Behavioral therapies are more commonly applied in the later stages of dementia, while modified cognitive-behavioral strategies appear to be more successful with those in the earlier stages of cognitive decline.

Behavior therapy requires a period of detailed assessment in which the triggers, behaviors and reinforcers (also known as the ABC: antecedents, behaviors and consequences) are identified, and their relationships made clear to the patient. Interventions are then based on an analysis of these findings. There are several interventions for patients with dementia based on behavior theory, including token economy, progressive muscle relaxation, imaging, and social skills training, to name a few[54]. However, most trials of such therapies do not focus on depression as an outcome. An exception is behavioral programming based on Lewinsohn's Pleasant Events model[56]. The model has three core components: (a) explaining the approach to the patient, emphasizing that a person's behavior is related to how he or she feels; (b) identifying pleasant and negative events in the patient's daily life, and assisting patients to work on increasing the first and decreasing the second; and (c) explaining that relaxation and mood monitoring are tools to assist the client in improving. Logsdon and Teri[57] constructed and validated a Pleasant Events Schedule—Alzheimer's Disease (PES-AD) to assist caregivers in implementing an intervention for patients with dementia. Teri and colleagues [58] applied this model to people with dementia, and found that depression scores improved in those who participated in a home-based program combining exercise with behavioral management training for caregivers, but the effects of the behavioral management component alone were not studied. Lichtenberg and colleagues[59] also examined the effect of a program based on this model on depression in nursing home residents with dementia. They found no differences on depression scores on either of two standard scales used, although statistically significant positive mood increases were noted.

Although cognitive-behavioral therapy (CBT) is more commonly used with caregivers of patients with dementia than with the patients themselves, a few studies have tested the effects individual or group CBT on BPSD, and on depression in particular. Teri and colleagues[60, 61] reported clinical improvements in depression scores on standardized

measures following CBT, using two strategies for treating Alzheimer's patients. Cognitive therapy was used with mildly demented adults to challenge the patient's negative cognitions in order to reduce distortions and enable the patient to generate more adaptive ways of viewing specific situations and events. Behavioral intervention, based on the Lewinsohn's Pleasant Events model described in the previous section of this paper, was used with more moderately or severely demented adults. Koder[62] also addressed the use of CBT techniques to treat anxiety in two cases of older patients with cognitive impairment, and reported positive results.

Other modifications to CBT, besides targeting cognitive strategies to early-stage dementia and behavioral strategies to later stages, involve reducing the cognitive load on the demented person by increasing repetition, utilizing concrete examples, and providing memory aids, such as cue cards. Implementing CBT with persons suffering from dementia also requires a highly structured format and continuous monitoring of the person's understanding of the therapeutic material. Also, most CBT programs for persons with dementia involve their caregivers, both as CBT "coaches" for the care recipient, and as treatment partners who often benefit from the intervention as well[53, 60, 62].

Early efforts have also been made to examine the efficacy of a related strategy, Problem-Solving Therapy (PST)[63], in treating depression in persons with cognitive deficits. Specially, Alexopolous and colleagues[64] observed improvements in depression following PST in persons with executive dysfunction, although persons with MMSE scores indicating MCI or dementia were screened out of the sample. A single case study[65] found that PST significantly improved the depression scores and clinical profile of an older patient with PD and MCI, both short and long-term (6 months post-treatment). However, further research on the implementation of PST in depressed persons with diagnosed MCI or dementia is needed.

Although there have been no methodologically rigorous trials of CBT or PST to treat depression in persons with dementia, interest in this topic has recently revived [66]. Stanley and colleagues[67] have recently received funding from NIMH to conduct a randomized controlled trial of the impact of CBT on anxiety in persons with mild to moderate dementia, and plan to measure depression using the Geriatric Depression Scale[68] as a secondary outcome, with results expected in 2010. In addition, Kiosses[69] is currently conducting an NIMH-funded trial of PST to treat depressed, cognitively impaired older adults, with results anticipated in 2011.

Sensory Stimulation Therapies

Sensory stimulation therapies that have been used to treat BPSD include art/music therapy, aromatherapy, animal-assisted/pet therapy, activity therapies, massage/touch therapies, and multisensory approaches (such as snoezelen). The goals of these therapies range from improvement of mood to increased health and improvement of memory. Similar to the emotion-oriented therapies, few rigorous studies have been performed, and results of efficacy are mixed, although reports from clinical observers are generally very positive. The impact of sensory stimulation therapies on depression in dementia has received limited attention, but their potential for efficacy appears positive.

Art therapy is theorized to provide people with dementia with meaningful stimulation, improved social interaction, and a chance to exercise personal choice[52]. Clinical observation of patients with dementia engaging in art therapy has indicated that it can provide pleasure and improve mood (REF). However, participants in an art therapy program recently studied by Rusted and colleagues[70] actually exhibited increased depression scores on two standardized measures over the course of a forty-week program, possibly due to feelings of failure in achieving a pleasing work of art. Reviews on art therapy in dementia[71] suggest

that further and more rigorous research is needed to assess its potential benefits on depression in this population.

Several clinical reports have described benefits gained by people with dementia from music therapy involving either listening or performing, although most involve listening[72]. Lord and Garner[73] found that a group of nursing home residents who regularly had music played to them, compared to a comparison group who did not, experienced higher levels of well-being, better social interaction, and improvements in autobiographical memory. More recently, Holmes and colleagues[74] randomized patients with moderate to severe dementia and diagnosed apathy to conditions of silent periods, prerecorded music, or live interactive music, and found much higher levels of positive engagement in the live music condition than the silence or recorded condition. Other studies support the beneficial effects of music therapy on various BPSD other than depression [75–81], indicating that this mode of intervention deserves further attention.

Aromatherapy is one of the fastest growing of all the complementary therapies [82]. It appears to have several advantages over the pharmacological treatments widely used for dementia, especially limitation of adverse effects from traditional pharmacotherapy. There have been some positive results from recent controlled trials which have shown statistically significant reductions in agitation, with excellent compliance and tolerability[83–85]. However, the type of aromatherapy oils tested, method of administration and outcome measures used varied widely across the few available studies, and depression has not been studied as an outcome. Further trials are needed before conclusions can be drawn on the effectiveness of aromatherapy for depression or other BPSD.

Animal-assisted therapy (AAT) has been reported to lessen agitation and improve socialization in patients with dementia in several small, uncontrolled trials[86, 87]. Two small studies [88, 89] reported reductions of apathy and withdrawal in dementia patients exposed to therapy dogs in a nursing home setting. However, in the only study that employed a measurement of depression[88], no significant changes in depression occurred. Further studies with larger samples and expanded measurement are needed. In their review of the limited literature available on AAT and dementia, Filan and Llewellyn-Jones[90] concluded that AAT may have positive effects on BPSD, but the duration of these effects is unknown, and studies are needed to disentangle the relative benefits gained from “visiting” animals versus “resident” animals. Possible interaction effects from dual exposure of patient and staff/caregivers to the animals during therapy also require further exploration.

Activity therapies include structured physical and recreational activities. A review of 27 studies by Eggermont and Scherder[91] concluded that physical activity programs can improve mood in patients with dementia, with a recent study[92] indicating that whole-body movement programs have a greater positive impact than walking alone. One study found that depression scores improved in people with dementia who participated in a home-based program combining exercise with behavioral management training for caregivers[58]; unfortunately, it is not possible to disentangle the effects of one intervention from the other. Another study with depression as an outcome[93] found that a biweekly exercise program improved ADL function in AD patients compared to controls over a one-year period, but had no impact on depression scale scores. These mixed results indicated that activity therapy may be beneficial for depression in dementia, but studies need to focus closely on the effects of specific types of activities.

A review of massage and touch interventions for dementia[94] found that the very limited amount of reliable evidence available supported massage and touch interventions for anxiety associated with dementia, especially hand massage for the immediate or short-term

reduction of agitated behavior. Cohen-Mansfield[95] reported decreases in anxiety in two small trials, one involving daily hand massage and therapeutic touch, and the other hand massage with essential oils. Unfortunately, no massage trials appear to have considered depression as an outcome variable. Massage therapy, like other CAM for dementia, requires further research to establish its efficacy in BPSD, including depression.

Multisensory approaches usually involve using a room designed to provide several types of sensory stimulation such as light (frequently in the form of moving flexible fiber optics), texture (cushions and vibrating pads), smell, or sound. The use of these resources is tailored to the individual and therefore not all of the available forms of stimulation may be used in one session. One such approach, Snoezelen, provides sensory stimuli to stimulate the primary senses of sight, hearing, touch, taste and smell, through the use of lighting effects, tactile surfaces, meditative music and the odor of relaxing essential oils. A review by Vervaik and colleagues[96] provides some evidence that Snoezelen/Multisensory stimulation in a multisensory room is effective in reducing apathy in late-stage dementia patients. A recent randomized controlled trial by Staal and colleagues[97] also found that patients on a geriatric psychiatric unit receiving Snoezelen and standard psychiatric care had reduced apathy and agitation scores, as well as increased activities of daily living, compared to patients receiving standard care alone. Although multisensory approaches to treatment of BPSD appear quite promising, there is a need for more research-based evidence to inform and justify the use of snoezelen and similar multisensory approaches in dementia care[98].

SUMMARY

A wide range of pharmacological and nonpharmacological treatments have been used to relieve depression in persons with cognitive impairment and dementia. Clinical consensus and research appear to support SSRIs as a first choice for the treatment of depression in dementia. In nonresponsive or special needs patients, other drugs have been used, including antipsychotics, anticholinergics, anticonvulsants, memantine, and complementary/alternative medications. Extra care is required in prescribing to this population, due to the generally high level of medical and psychiatric comorbidity and potential difficulty in assessing the cognitively impaired patient's response.

Nonpharmacologic interventions including emotion-oriented therapies, behavioral and cognitive-behavioral modification programs, and structured activity programs demonstrate initial support for treating depression, anxiety, and other BPSD. Sensory stimulation therapies such as art/music therapy, aromatherapy, animal-assisted/pet therapy, activity therapies, massage/touch therapies, and multisensory approaches show some promise for successful treatment of depression in dementia, but further and more rigorous research is needed to establish their validity.

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