JACOBS PUBLISHERS

OPEN ACCESS

Jacobs Journal of Internal Medicine

Review Article

The Urgent and Unmet Need for Safe and Effective Treatment of Agitation

Joseph V. Pergolizzi Jr., MD[1], Robert B. Raffa PhD[2], Joseph Pergolizzi III[1] , Gianpietro, Zampogna MD [1,3] , Charles Fleischer MD[1] , Robert Taylor PhD[1] and Jo Ann LeQuang BA[1*]

[1]*NEMA Research, Inc., Naples, FL*

[2]*University of Arizona College of Pharmacy, Tucson, AZ*

[3]*Department of Medicine, St. Vincent Charity Medical Center/ Case Western Reserve University School of Medicine, Cleveland, OH*

**Corresponding author: Dr. Jo Ann LeQuang BA, 1216 N. Velasco Street, Suite J, Angleton, TX 77515, Tel: (979)864-4479, Email: joann@leqmedical.com*

Received: 10-21-2016

Accepted: 01-12-2017

Published: 02-03-2017

Abstract

Agitation may occur in many settings: upon emergence from anesthesia, in the context of certain mental illnesses, secondary to brain injury or substance abuse, as a side effect of medication, and with certain forms of cognitive impairment. Agitation occurs frequently in patients with dementia, including but not limited to Alzheimer's disease. This neuropsychiatric symptom is likely related to dysfunctional neurotransmissions, but the exact mechanisms remain unknown. There is no FDA-approved treatment for agitation but several agents are used off-label to help manage agitation, which can be a chronic and troublesome condition in patients with dementia. Antipsychotics, antidepressants, opioid analgesia, cannabinoids, antiepileptic agents, dextromethorphan, scyllo-inositol, brexipiprazole, and prazosin are discussed as possible treatments in the literature. The effectiveness of many pharmacological interventions for agitation can be equivocal and safety issues are of concern. Nonpharmacological interventions, such as music therapy, aromatherapy, and animal-assisted therapy, have reported modest success but may be difficult to implement emergency departments as well as in some institutionalized settings. As the geriatric population in developed nations increases, agitation secondary to various forms of dementia will likely increase as well. Agitation can pose risks to patients and their caregivers and there is an urgent unmet medical need to find safe, effective treatments.

Introduction

Neuropsychiatric symptoms remain challenging to treat. These behavioral symptoms can be distressing to patients, extraordinarily burdensome to caregivers, and costly to the healthcare system as extensive neuropsychiatric symptomology is associated with increased risk of institutionalization [1]. Agitation, a neuropsychiatric symptom, may occur in the context of apathy, depression, anxiety, and restlessness [2]. As early as 1989 agitation was defined as "inappropriate verbal, vocal, or motor activity that is not explained by needs or confusion, per se."[3] Agitation is associated with excessive psychomotor activity, emotional distress, aggressive behaviors, disruptive irritability, and disinhibition [4]. Agitated individuals may wander, cry out, complain, use foul language, display aggressive behaviors or repetitive movements, and be uncooperative, negative, and disruptive [3]. Agitation increases the patient's risk of injury and reduces his or her quality of life [1].

Agitation may present secondary to mental illness (such as bipolar disorder or schizophrenia) or brain trauma; it may also occur as a side effect of certain medications or as a result of emergence from anesthesia; it is often observed in patients with dementia. Thus, agitation may present as a medical emergency, as a relatively predictable response (such as anesthesia emergence), or as an ongoing chronic condition. The latter is perhaps the most troubling manifestation for agitation and requires strategies for long-term management. Agitation is a persistent and frequent comorbid condition for patients with Alzheimer's disease (AD) and has been associated with adverse consequences in this population [4]. Agitation is also

among the many anxiety-related symptoms associated with Parkinson's Disease [5] (Lewy body dementia) and it occurs in other patient populations with cognitive disorders. In fact, agitation may affect as many as 70% of dementia patients. Its link to AD makes the need for a better understanding of agitation crucial, in that AD affects over 35 million people worldwide and its prevalence is likely to increase as industrialized populations age [6]. AD is associated with a range of neuropsychiatric symptoms associated with behavior and psychological changes in the patient. Some of the hallmark symptoms of AD include agitation, anxiety, apathy, aggression, delusions, and hallucinations [7]. These neuropsychiatric symptoms are often persistent and are associated with morbidity, mortality, and substantially increased healthcare utilization [8].

The International Psychogeriatric Association (IPA) recently proposed a consensus definition for agitation in patients with cognitive disorders. The IPA states that agitation commonly occurred in patients with cognitive impairment or dementia who exhibit behaviors consistent with emotional distress, manifested in the form of excessive motor activity and/or verbal or physical aggression; and evidenced by behaviors that caused excess disability and could not be solely attributable to another disorder, such as a psychiatric condition or a substance-related problem [9].

While several studies have explored potential treatment options for agitation, many of the older studies are small with considerable heterogeneity in design, making it difficult to draw strong conclusions [10]. Fortunately, more recent studies exhibit robust design.

Our aim in this article is to better understand agitation in this setting and its possible treatments. To this end, we conducted a search of the literature which we present as a narrative review.

Mechanisms of Agitation

The entire spectrum of neuropsychiatric symptoms are likely associated with the body's neurotransmitter systems (e.g., serotonergic, noradrenergic, cholinergic, dopaminergic, opioid, cannabinoid, amino acid, etc.), such that dysfunction in any or a combination of these neurotransmission systems might create an imbalance in the brain networks that handle affective and executive functions [11]. Further, there is likely involvement of neuro-inflammatory processes and changes in the neurotransmitters themselves, that is, serotonin, glutamate, sigma-1, and cannabinoids. Thus, if a disease process erodes the body's ascending serotonergic pathways, it is likely that this erosion will disrupt the brain's afferent brain monoamine system, which, in turn, will impair the proper function of interconnecting pathways, such as the serotonergic-dopaminergic axis [12]. From these hypotheses, investigators are identifying many potential new areas of research and targets for drug development.

Among other examples, the role of the α_1-adrenoceptors is being investigated as being important in better treating agitation. In a study of postmortem brain tissue from 24 Alzheimer's disease patients versus 25 comparison cases, aggressive behavior could be significantly correlated with elevated numbers of the α_1-adrenoceptors, suggesting that upregulation of the the α_1-adrenoceptor system is associated with aggressive behaviors [13].

Treatment of Agitation

The Food and Drug Administration (FDA) has not approved any drug for the treatment of agitation, and in the European Union (EU) only risperidone (an antagonist at multiple dopamine, serotonin, and adrenergic receptor subtypes) is approved for the short-term treatment of aggression in AD patients [11]. Without a pharmacological arsenal and with only limited evidence, it becomes extremely challenging for clinicians to manage agitation effectively. Furthermore, the potentially effective agents for treating agitation are associated with serious safety concerns [4]. Since agitation is a serious symptom that can cause considerable problems for caregivers and great distress, even morbidity, to the patient, this lack of effective treatment represents what can only be called an urgent unmet need.

In the United States agitation is sometimes treated with the off-label use of antipsychotics, sedatives/hypnotics, anxiolytics, acetylcholinesterase inhibitors, memantine (an antagonist of NMDA [*N*-Methyl-D-aspartate] subtype of glutamate receptors) and antidepressants. However, these agents are associated with a high rate of side effects, some of which can be serious and are potentially treatment limiting [11]. Since many agitation patients are elderly, and may have comorbid conditions, identifying the appropriate pharmacological treatment can be particularly challenging. Nonpharmacological treatment options exist and some have demonstrated modest success but may not always be practical, particularly in large institutionalized settings [14].

In patients with dementia or other forms of cognitive impairment (including but not limited to AD), agitation symptoms may change—and change often—over the course of illness [15, 16]. By the same token, some patients will experience agitation only briefly and then symptoms will resolve spontaneously. Thus, the treatment of agitation must be highly individualized. In hospitals or long-term care facilities, the use of pharmacological agents may be administered to prevent the patient from harming himself or others and should be carefully documented.

Pharmacological Treatments

Antipsychotics

Antipsychotic agents are sometimes used to treat agitation,

but their effectiveness is unclear and there are known serious safety concerns [8]. Antipsychotic drugs carry black-box warnings [17] and are associated with adverse events including drowsiness, weight gain, falls and associated injuries, and increased mortality [18]. Nevertheless, in the U.S., antipsychotic agents are used off-label to treat agitation; their role in agitation treatment is likely borne out of pragmatic clinicians facing urgent situations with few options. Studies of antipsychotics in the treatment of agitation have shown equivocal or, at best, modestly favorable results which must be weighed against their considerable risks [19-26].

Haloperidol is a neuroleptic agent that is used to treat psychosis and is frequently administered to demented patients to treat symptoms associated with psychosis. It has multiple receptor binding and intrinsic activities, including as an antagonist at multiple dopamine, serotonin, adrenergic, and other receptor subtypes. A meta-analysis of studies about the effectiveness of haloperidol to treat agitation in this population found it did not improve symptoms of agitation versus placebo and had a high rate of adverse events, including treatment-limiting side effects [23]. Compared to individuals not taking haloperidol, matched patients taking haloperidol had an increased mortality risk of 3.8% (95% confidence interval [CI], 1.0% to 6.6%, p<0.01) with a number-needed-to-harm (NNH) of 26 (95% CI, 15 to 99) [27]. Substantial risks occur in other drugs of this class: the NNH numbers for risperidone, olanzapine, and quetiapine are 27, 40, and 50, respectively [27]. The use of psychotropic agents (including antipsychotics as well as anxiolytics and antidepressants) may be inappropriate in elderly patients, but a prospective multicenter study found they were prescribed to 57.5% of geriatric patients [28]. Indeed, potentially inappropriate prescribing occurs in the majority (63.2%) of community-dwelling older patients [29].

Antidepressants

Antidepressant agents have broad clinical effects in the treatment of many psychiatric conditions, including distress, anxiety, depression, and agitation. The older-generation antidepressants (so-called tricyclic antidepressants or TCAs) inhibit the presynaptic neuronal reuptake of serotonin and norepinephrine, but also bind to multiple receptor sites, and are associated with anticholinergic side effects and potential cardiac toxicity. Newer Selective Serotonin Reuptake Inhibitors are considered relatively safer, but are still associated with potentially severe adverse events such as gastrointestinal (GI) bleeding [30], hyponatremia [31], and falls with related fractures [32].

Antidepressants are widely used in patients with dementia in real-world clinical practice. In a survey of demented patients, it was found that 44% were being treated with antidepressants to address their various neuropsychiatric symptoms [33]. Despite the use of antidepressants in this population, little is known about their safety and efficacy in dementia patients suffering from agitation [34].

Citalopram is a new SSRI that is often prescribed in geriatric patients [35, 36] and has been used for a considerable time off-label as a treatment for agitation and aggression associated with dementia [37]. A few smaller studies have demonstrated the effectiveness of citalopram in treating agitation and related symptoms of dementia [38-40]. Citalopram appears to improve functional serotonergic neurotransmission [11]. In a double-blind, parallel-group multicenter trial of 186 AD patients, the subjects were randomized to receive 30 mg/day of citalopram or placebo for nine weeks (dosage was titrated to 30 mg/day over first three weeks of the study) [41]. As agitation was an inclusion criterion, it was present in 100% of patients at baseline. The heterogeneity of response to treatment was organized by investigators into 10 subgroups. Citalopram was more effective in patients who were outpatients, had a lesser degree of cognitive impairment, had moderate rather than severe agitation, and were in the age group between 76 and 82 years. By contrast, placebo was more effective in patients in long-term care, in those with more severe cognitive impairment, in those with more severe agitation, and in patients treated concurrently with lorazepam [41]. There also appears to be genetic variation in response to citalopram. In a nine-week randomized, double-blind, placebo-controlled study of AD patients with agitation treated with citalopram or placebo, citalopram demonstrated a slight but significant benefit in patients with the genetic variations of *HTR2A* and *HTR2C* loci [42].

The Citalopram for Agitation in Alzheimer's Disease study evaluated the effects of citalopram on 12 neuropsychiatric symptom domains associated with Alzheimer's disease, including agitation [43]. Using the Neuropsychiatry Inventory (NPI), caregivers reported scores after patients had received 30 mg/day citalopram or placebo for nine weeks. At nine weeks, the citalopram patients were significantly less likely to be observed having symptoms of delusions (odds ratio [OR] 0.40), anxiety (OR=0.43), irritability/lability (OR 0.38) and median scores showed significant improvement in citalopram patients compared to placebo patients for hallucinations and sleep or nighttime behavior disorders. The effect of citalopram on agitation was measured by the Neurobehavioral Rating Scale (NRS) and a modified CGIC. In a secondary analysis of the study, it was shown that citalopram patients were as likely to have reports of agitation or aggression at week 9 as placebo patients (OR=0.63, not significant) [43]. All patients in this study were exposed to a psychosocial intervention for treatment of neurobehavioral symptoms and it has been speculated the relatively robust placebo response observed in the study might have been in part due to the psychosocial intervention [44].

In a study of 186 patients, citalopram 30 mg/day significantly

reduced agitation (and also reduced distress reported in caregivers) [4]. In this study, 40% of the patients treated with citalopram were deemed to be "much" or "very much" improved versus 26% of placebo patients. However, citalopram patients also exhibited cognitive worsening and prolonged QT-interval, which may limit the use of citalopram for agitation [4]. Current prescribing recommendations by the FDA for citalopram are 20 mg/day for patients over the age of 60 owing to the potential for prolonged QT-intervals which can be associated with potentially life-threatening arrhythmic events [45]. Thus, the 30 mg/day citalopram dose in this study exceeds the FDA recommended dose of 20 mg/day for patients aged 60 and older [46], limiting the utility of this dose in the geriatric population.

The potential benefits of citalopram on agitation may be in part due to its sedative effects. A study using the Citalopram for Agitation in Alzheimer's Disease study data found a statistically significant mediating effect of sedation on agitation outcomes, but the magnitude of effect was small (effect size 0.16, 95% CI, 0.08 to 0.22) [47].

Treatment-emergent suicidal ideation in geriatic patients has been associated with antidepressant therapy and in a retrospective analysis of data from 233 clinical trial patients with major depression and without baseline suicidal ideation taking venlafaxine XR for 12 weeks, suicidal ideation occurred in 10% of subjects [48]. The use of antidepressant therapy in the elderly must be approached with caution.

Opioids

The role of opioids for the treatment of agitation associated with dementia has not been elucidated and to the best of the authors' knowledge, no randomized placebo-controlled trials of opioids for agitation in dementia have been reported to date [49]. Opioids bind to specific seven-transmembrane G protein-coupled receptors (7TM-GPCRs). They inhibit presynaptic Ca^{2+} influx and hyperpolarize post-synaptic neurons. An intriguing study designed as a cluster randomized clinical trial (n=352 in 60 clusters in 18 nursing homes) found that many verbal agitation behaviors (negativity, complaining, use of foul language, repetitious sentences, constant demands for attention, and so on) in severely demented nursing home patients responded favorably to analgesics, which also improved symptoms of restlessness and pacing [50]. The link between inadequate analgesia and agitation warrants further study [51]. The link between analgesia and anxiety is established and is illustrated by the fact that nursing home patients requesting an anxiolytic agent must have a pain assessment performed prior to the nurse's offering the anxiolytic agent [52].

Cannabinoids

Cannabinoids may exert a neuroprotective effect that makes them of interest for the treatment of agitation. The body's endogenous cannabinoid system acts at two main 7TM-GPCR cannabinoid receptors, CB1 and CB2. CB1 receptors are located throughout the central nervous system, and are particularly dense in the regions of the hippocampus, basal ganglia, and cerebellum, while CB2 receptors are principally found in the peripheral nervous system. THC (Δ^9-tetrahydrocannabinol) is a psychoactive compound that activates CB1 and, to a lesser extent, CB2 receptors and, in so doing, inhibits the release of neurotransmitters within the brain and regulates synaptic transmissions. The exact mechanisms remain to be elucidated, but it appears that cannabinoids can reduce excitotoxicity by regulating glutamate and possibly by controlling neuro-inflammation [53]. The cannabinoid receptor agonist dronabinol has been used with success in improving agitation and nocturnal agitation in dementia patients [53]. The clinical use of cannabinoids is not addressed in the Federal Controlled Substances Act [54].

Antiepileptic Drugs

Antiepileptic drugs, also known as anticonvulsants, have long been used to treat numerous non-epilepsy disorders [55]. Most antiepileptic agents have more than one mechanism of action and modulate the ϒ-aminobutyric acid (GABA)ergic and glutamergic neurotransmission systems, which may explain their effectiveness in treating neuropsychiatric conditions [56].

The off-label use of antiepileptic drugs to treat agitation related to dementia and other cognitive disorders typically occurs only after first-line and subsequent treatments have failed?. Carbamazepine may have the best evidence for use in dementia-associated agitation, although there are tolerability issues to consider [57]. There is limited evidence in support of gabapentin, oxcarbazepine, and topiramate for effectiveness in treating agitation [58]. Valproic acid, an older-generation anticonvulsant, has been used to treat symptoms associated with dementia, but a recent meta-analysis found that valproate preparations were not effective in treating agitation among demented patients [1]. Furthermore, valproate formulations have relatively high rates of adverse effects.

Dextromethorphan Hydrobromide

Dextromethorphan is a high-affinity sigma-1 receptor agonist, which allows it to inhibit glutamate release at the pre-synaptic level. Further, it can modulate postsynaptic glutamate response by acting as a low-affinity NMDA receptor agonist. Dextromethorphan is also a serotonin and norepinephrine reuptake inhibitor [59]. When taken concurrently, quinidine increases the bioavailablity of dextromethorphan [59]. Dextromethorphan in combination with low-dose quinidine is indicated for treating pseudobulbar affect which may occur secondary to dementia, traumatic brain injury, or stroke, among

other conditions [60].

In a phase II randomized, multicenter, double-blind, placebo-control, parallel-group study over five weeks, Alzheimer's disease patients with clinically significant agitation were enrolled (n=1,220) and randomized to receive dextromethorphan plus quinidine or placebo in stage 1 of the study; in stage 2, the dextromethorphan group continued on that regimen while placebo patients were stratified by response and then re-randomized in a 1:1 scheme to dextromethorphan plus quinidine (n=59) or placebo (n=60) [61]. Agitation and aggression were measured on the Neuropsychiatric Inventory (NPI). In stage 1 of the study, mean NPI agitation/aggression scores dropped from 7.1 at baseline to 3.8 in the dextromethorphan group compared to 7.0 to 5.3 in the placebo group. The treatment differences between groups were significant in stage 1 ($p<0.001$). In the second stage of the study, NPI scores dropped from 5.8 to 3.8 in the dextromethorphan group and 6.7 to 5.8 in the placebo group (between groups $p=0.02$). Adverse events included falls (8.6% vs. 3.9%), diarrhea (5.9% vs. 3.1%) and urinary tract infections (5.3% vs. 3.9%) for dextromethorphan and placebo, respectively with more serious advents occurring the active treatment arm than placebo (7.9% vs. 4.7%). However, dextromethorphan was not associated with cognitive impairment, sedation, or clinically relevant prolongation of the QT-interval [61].

Scyllo-inositol

Scyllo-inositol (also known as ELKND005 and other names), a stereoisomer of inositol, is a naturally occurring plant sugar with a mechanism of action not fully known but that appears to enhance synaptic activity. On the one hand, it regulates the brain's myoinositol metabolism and related phosphoinositol signaling and, on the other hand, it protects the brain from oligomer-induced toxicity associated with β-amyloid anti-aggregation effects [62]. Its potential role in the treatment of agitation remains to be elucidated.

Brexpiprazole

Derived from quinolinone and related to aripiprazole, brexpiprazole is a dopamine-receptor partial agonist with broad action over multiple monoamine systems. It acts as a partial agonist at D2, D3 and 5-HT_{1A} receptors and as an antagonist at 5-HT_{2Q} and α_1-adrenoceptors [63]. Brexpiprazole may be considered a promising new molecule for treating symptoms of AD, including but not limited to agitation.

Prazosin

Dementia-related agitation and aggression may be related to enhanced responsiveness to norepinephrine at the α_1-adrenoceptors. Prazosin is a central the α_1-adrenoceptor antagonist and has been approved to treat sleep disturbances associated with post-traumatic stress disorders, among other conditions [64].

In a double-blind, placebo-controlled, parallel-group study, 22 patients with probable or possible AD and agitation/aggression were randomized to receive prazosin (initiated at 1 mg/day and titrated up to 6 mg/day in a flexible dosing algorithm) or placebo [64]. The Brief Psychiatric Rating Scale (BPRS) and NPI were used at weeks 1, 2, 4, 6, and 8 to assess symptoms. Those patients taking prazosin (mean dose 5.7 ± 1.2 0.9 mg/day) showed greater improvements than placebo patients on the NPI and BPRS scales with similar adverse effects.

Nonpharmacological Treatments

Nonpharmacological strategies to help manage agitation include the education of caregivers (training them in problem solving and psychosocial interventions to help address specific behaviors), understanding triggers for agitation, and training caregivers to proactively meet patient needs with respect to such things as hunger, thirst, pain, boredom, and issues of abandonment or loneliness [8,14]. Occupational therapy as part of a multidisciplinary team may improve neuropsychiatric symptoms in a clinical setting [65].

Aromatherapy with essential melissa oil was evaluated in a study of 72 patients suffering from severe dementia with agitation [66]. Patients were randomized into two groups, one exposed to melissa balm oil, the other sunflower oil (placebo). Changes in agitation were measured on the Cohen-Mansfield Agitation Inventory (CMAI) over a four-week period. A 30% or greater reduction in CMAI score occurred in 60% of melissa and 14% of control patients and overall improvement in agitation (mean reduction in CMAI score) occurred in 35% of melissa and 11% of placebo patients ($p<0.0001$) with quality of life indices improved in the active treatment arm as well ($p=0.005$) [66]. No significant side effects occurred in either group. There is also some weak evidence that person-centered care initiatives, sensory therapy activities, and structured music therapy may also reduce agitation [67]. In nursing home residents suffering from dementia and neuropsychiatric symptoms including agitation, animal-assisted interventions (AAI) found that animal therapy with dogs improved quality of life in patients with severe dementia but did not reduce agitation [2]. Nonpharmacological therapy may be employed as first-line treatment but can also be used in combination with drug therapy [11]. Nonpharmacological treatments are often safe and well tolerated by patients but may pose challenging demands on staff caring for institutionalized patients. When such interventions are appropriate, they should be accompanied by comprehensive staff education and periodic re-training efforts.

Discussion

Agitation presents to clinicians in different forms: it may be a medical emergency (such as a schizophrenia-related episode of agitation), side effects of a medication, a symptom of brain injury, or a persistent condition comorbid with cognitive impairment. The latter manifestation is of particular concern, because as populations of the developed world age, the prevalence of age-related cognitive disorders, including but not limited to AD, is likely to increase substantially. There is no clear consensus as to how to best treat agitation in cognitively impaired patients, many of whom may be elderly and have other comorbid conditions that further complicate care. Although not always discussed in this context, agitation can be extremely distressing and even dangerous to caregivers and may result in institutionalization of patients who might otherwise have been appropriate candidates for home care.

A number of medications are available and used in the treatment of agitation, but pharmacological therapy can be limited by issues of tolerability and toxicity. Much remains to be learned about agitation. For example, can we identify different types of agitation and the best treatment options for each type? Can we stratify patients, particularly the mentally ill and cognitively impaired, for their risk of agitation? Will different types of agitation respond to different pharmacological interventions?

At present, there is an urgent unmet medical need for better pharmacological therapies for agitation. With this comes a parallel urgent need for greater clinician education as to the nature of agitation and how to treat it. Since many drugs already exist and are in use (largely off-label) in the treatment of agitation, it may be that further study will help clarify prescribing choices. Greater study of the brain and neurotransmissions systems may reveal new therapeutic targets.

Conclusion

Agitation is a prominent and prevalent neuropsychiatric symptom which may occur in the setting of mental illness, brain injury, or in patients suffering from dementia, including but not limited to AD. In these latter patients, agitation may be a chronic and particularly troublesome condition. Despite its ubiquity, there is no approved pharmacological therapy for agitation, and off-label use of antidepressants, antipsychotics, and other drugs are associated with tolerability issues or safety concerns, including an elevated risk of mortality. There is an urgent unmet need to find safe, effective treatments for agitation.

References

1. Lonergan E, Luxenberg J. Valproate preparations for agitation in dementia. Cochrane Database Syst Rev. 2009, (3): CD003945.

2. Olsen C, Pedersen I, Bergland A, Enders-Slegers MJ, Patil G et al. Effect of animal-assisted interventions on depression, agitation and quality of life in nursing home residents suffering from cognitive impairment or dementia: a cluster randomized controlled trial. Int J Geriatr Psychiatry. 2016, 31(12): 1312-1321.

3. Cohen-Mansfield J, Marx M, Rosenthal A. A description of agitation in a nursing home. J Gerontol (Med Sci). 1989, 44(3): M77-M84.

4. Porsteinsson AP, Drye LT, Pollock BG, Devanand DP, Frangakis C et al. Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. JAMA. 2014, 311(7): 682-691.

5. Dissanayaka NN, O'Sullivan JD, Pachana NA, Marsh R, Silburn PA et al. Disease-specific anxiety symptomatology in Parkinson's disease. Int Psychogeriatr. 2016, 28(7): 1153-1163.

6. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W et al. The global prevalence of dementia: a systematic review and meta-analysis. Alzheimers Dement. 2013, 9(1): 63-75.

7. McKeith I, Cummings J. Behavioural changes and psychological symptoms in dementia disorders. Lancet Neurol. 2005, 4(11): 735-742.

8. Kales HC, Gitlin LN, Lyketsos CG, Detroit Expert Panel on A, Management of Neuropsychiatric Symptoms of D. Management of neuropsychiatric symptoms of dementia in clinical settings: recommendations from a multidisciplinary expert panel. J Am Geriatr Soc. 2014, 62(4): 762-769.

9. Cummings J, Mintzer J, Brodaty H, Sano M, Banerjee S et al. Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. Int Psychogeriatr. 2015, 27(1): 7-17.

10. Soto M, Andrieu S, Nourhashemi F, Ousset PJ, Ballard C et al. Medication development for agitation and aggression in Alzheimer disease: review and discussion of recent randomized clinical trial design. Int Psychogeriatr. 2014: 1-17.

11. Antonsdottir IM, Smith J, Keltz M, Porsteinsson AP. Advancements in the treatment of agitation in Alzheimer's disease. Expert Opin Pharmacother. 2015, 16(11): 1649-1656.

12. Geda YE, Schneider LS, Gitlin LN, Miller DS, Smith GS et al. Neuropsychiatric symptoms in Alzheimer's disease: past progress and anticipation of the future. Alzheimers Dement. 2013, 9(5): 602-608.

13. Sharp SI, Ballard CG, Chen CP, Francis PT. Aggressive behavior and neuroleptic medication are associated with increased number of alpha1-adrenoceptors in patients with Alzheimer disease. Am J Geriatr Psychiatry. 2007, 15(5): 435-437.

14. Gitlin LN, Kales HC, Lyketsos CG. Nonpharmacologic management of behavioral symptoms in dementia. JAMA. 2012, 308(19): 2020-2029.

15. Steinberg M, Tschanz J, Corcoran C, Steffens DC, Norton MC et al. The persistance of neuropsychiatric symptoms in dementia: the Cache County Study. Int J Geriatr Psychiatry. 2004, 19(1): 19-26.

16. Savva G, Zaccai J, Matthews F, Davidson JE., McKeith I et al. Prevalence, correlates, and course of behavioral and psychological symptoms of dementia in the population. The British Journal of Psychiatry. 2009, 194(3): 212-219.

17. Small GW. Treating dementia and agitation. JAMA 2014, 311(7): 677-678.

18. Drye LT, Ismail Z, Porsteinsson AP, Rosenberg PB, Weintraub D et al. Citalopram for agitation in Alzheimer's disease: design and methods. Alzheimers Dement. 2012, 8(2): 121-130.

19. Ballard C, Howard R. Neuroleptic drugs in dementia: benefits and harm. Nat Rev Neurosci. 2006, 7(6): 492-500.

20. Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. Am J Geriatr Psychiatry. 2006, 14(3): 191-210.

21. Schneider LS, Pollock VE, Lyness SA. A metaanalysis of controlled trials of neuroleptic treatment in dementia. J Am Geriatr Soc. 1990, 38(5): 553-563.

22. De Deyn PP, Rabheru K, Rasmussen A, Bocksberger JP, Dautzenberg PL et al. A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. Neurology. 1999, 53(5): 946-955.

23. Lonergan E, Luxenberg J, Colford J. Haloperidol for agitation in dementia. Cochrane Database Syst Rev. 2001(4): CD002852.

24. Ballard C, Thomas A, Gerry S, Yu LM, Aarsland D et al. A double-blind randomized placebo-controlled withdrawal trial comparing memantine and antipsychotics for the long-term treatment of function and neuropsychiatric symptoms in people with Alzheimer's disease (MAIN-AD). J Am Med Dir Assoc. 2015, 16(4): 316-322.

25. Ballard C, Corbett A, Chitramohan R, Aarsland D. Management of agitation and aggression associated with Alzheimer's disease: controversies and possible solutions. Curr Opin Psychiatry. 2009, 22(6): 532-540.

26. Teri L, Logsdon RG, Peskind E, Raskind M, Weiner MF et al. Treatment of agitation in AD: a randomized, placebo-controlled clinical trial. Neurology. 2000, 55(9): 1271-1278.

27. Maust DT, Kim HM, Seyfried LS, Chiang C, Kavanagh J et al. Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. JAMA Psychiatry. 2015, 72(5): 438-445.

28. Vidal X, Agusti A, Vallano A, Formiga F, Moyano AF et al. Elderly patients treated with psychotropic medicines admitted to hospital: associated characteristics and inappropriate use. Eur J Clin Pharmacol. 2016, 72(6): 755-764.

29. Nicieza-Garcia ML, Salgueiro-Vazquez ME, Jimeno-Demuth FJ, Manso G. Beers versus STOPP criteria in polyharmacy community-dwelling older patients. Farm Hosp. 2016, 40(3): 150-164.

30. van Walraven C, Mamadani M, Wells P, Williams J. Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study. BMJ. 2001, 323(7314): 655-658.

31. Fabian T, Amico J, Kroboth P, Mulsant BH, Corey SE et al. Paroxetine-induced hyponatremia in older adults. Arch Intern Med. 2004, 164(3): 327-332.

32. Richards J, Papaioannou A, Adachi J, Joseph L, Whitson HE et al. Effect of selective serotonin reuptake inhibitors on the risk of fracture. Arch Intern Med. 2007, 167(2): 188-194.

33. Iden K, Engedal K, Hjorleifsson S, Ruth S. Prevalence of depression among recently admitted long-term care patients in Norwegian nursing homes: association with diagnostic work-up and use of antidepressants. Dement Geriatr Cogn Disord. 2014, 37 (3-4): 154-162.

34. Seitz DP, Adunuri N, Gill SS, Gruneir A, Herrmann N et al. Antidepressants for agitation and psychosis in dementia. Cochrane Database Syst Rev. 2011, 16 (2): CD008191.

35. Bergh S, Selbaek G, Engedal K. Discontinuation of antidepressants in people with dementia and neuropsychiatric symptoms (DESEP study): double blind, randomised, parallel group, placebo controlled trial. BMJ. 2012, 344: e1566.

36. Coupland C, Dhiman P, Morriss R, Arthur A, Barton G et al. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. BMJ. 2011, 343: d4551.

37. Nyth AL, Gottfries CG. The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders. A Nordic multicentre study. Br J Psychiatry. 1990, 157: 894-901.

38. Pollock BG, Mulsant BH, Rosen J, Sweet RA, Mazumdar S, et al. Comparison of citalopram, perphenazine, and placebo for the acute treatment of psychosis and behavioral disturbances in hospitalized, demented patients. Am J Psychiatry. 2002, 159(3): 460-465.

39. Pollock BG, Mulsant BH, Sweet R, Burgio LD, Kirshner MA et al. An open pilot study of citalopram for behavioral disturbances of dementia. Plasma levels and real-time observations. Am J Geriatr Psychiatry. 1997, 5(1): 70-78.

40. Pollock BG, Mulsant BH, Rosen J, Mazumdar S, Blakesley RE et al. A double-blind comparison of citalopram and risperidone for the treatment of behavioral and psychotic symptoms associated with dementia. Am J Geriatr Psychiatry. 2007, 15(11): 942-952.

41. Schneider LS, Frangakis C, Drye LT, Devanand DP, Marano CM et al. Heterogeneity of Treatment Response to Citalopram for Patients With Alzheimer's Disease With Aggression or Agitation: The CitAD Randomized Clinical Trial. Am J Psychiatry. 2016, 173(5): 465-72.

42. Peters ME, Vaidya V, Drye LT, Devanand DP, Mintzer JE et al. Citalopram for the Treatment of Agitation in Alzheimer Dementia: Genetic Influences. J Geriatr Psychiatry Neurol. 2016, 29(2): 59-64.

43. Leonpacher AK, Peters ME, Drye LT, KM Makino, JA Newell et al. Effects of Citalopram on Neuropsychiatric Symptoms in Alzheimer's Dementia: Evidence From the CitAD Study. Am J Psychiatry. 2016, 173(5): 473-480.

44. Rosenberg PB, Drye LT, Porsteinsson AP, Pollock BG, Devanand DP et al. Change in agitation in Alzheimer's disease in the placebo arm of a nine-week controlled trial. Int Psychogeriatr. 2015, 27(12): 2059-2067.

45. FDA. Abnormal heart rhythms associated with high doses of Clexa (citalopram hydrobromide). FDA Drug Safety Communication 2012.

46. Drye LT, Spragg D, Devanand DP, Frangakis C, Marano C et al. Changes in QTc interval in the citalopram for agitation in Alzheimer's disease (CitAD) randomized trial. PloS one. 2014, 9(6): e98426.

47. Newell J, Yesavage JA, Taylor JL, Kraemer HC, Munro CA et al. Sedation mediates part of Citalopram's effect on agitation in Alzheimer's disease. J Psychiatr Res. 2016, 74: 17-21.

48. Cristancho P, O'Connor B, Lenze EJ, Blumberger DM, Reynolds CF 3rd et al. Treatment Emergent Suicidal Ideation in depressed older adults. Int J Geriatr Psychiatry. 2016.

49. Brown R, Howard R, Candy B, Sampson EL. Opioids for agitation in dementia. Cochrane Database Syst Rev. 2015, (5): CD009705.

50. Husebo BS, Ballard C, Cohen-Mansfield J, Seifert R, Aarsland D. The response of agitated behavior to pain management in persons with dementia. Am J Geriatr Psychiatry. 2014, 22(7): 708-717.

51. Husebo BS, Ballard C, Aarsland D. Pain treatment of agitation in patients with dementia: a systematic review. Int J Geriatr Psychiatry. 2011, 26(10): 1012-1018.

52. Lapane KL, Quilliam BJ, Chow W, Kim MS. Impact of revisions to the F-Tag 309 surveyors' interpretive guidelines on pain management among nursing home residents. Drugs Aging. 2012, 29(5): 385-393.

53. Ramirez BG, Blazquez C, Gomez del Pulgar T, Guzman M, de Ceballos ML. Prevention of Alzheimer's disease pathology by cannabinoids: neuroprotection mediated by blockade of microglial activation. J Neurosci. 2005, 25(8): 1904-1913.

54. Drug Enforcement Administration DoJ. List of Controlled Substances. 2015.

55. Johannessen Landmark C. Antiepileptic drugs in non-epilepsy disorders: relations between mechanisms of action and clinical efficacy. CNS drugs. 2008, 22(1): 27-47.

56. Bialer M. Why are antiepileptic drugs used for nonepileptic conditions?. Epilepsia. 2012, 53 Suppl 7: 26-33.

57. Gallagher D, Herrmann N. Antiepileptic drugs for the treatment of agitation and aggression in dementia: do they have a place in therapy?. Drugs. 2014, 74(15): 1747-1755.

58. Guay DR. Newer antiepileptic drugs in the management of agitation/aggression in patients with dementia or developmental disability. Consult Pharm. 2007, 22(12): 1004-1034.

59. Pope LE, Khalil MH, Berg JE, Stiles M, Yakatan GJ et al. Pharmacokinetics of dextromethorphan after single or multiple dosing in combination with quinidine in extensive and poor metabolizers. J Clin Pharmacol. 2004, 44(10): 1132-1142.

60. Hammond FM, Alexander DN, Cutler AJ, Amico SD, Doody RS et al. PRISM II: an open-label study to assess effectiveness of dextromethorphan/quinidine for pseudobulbar affect in patients with dementia, stroke or traumatic brain injury. BMC neurology. 2016, 16: 89.

61. Cummings JL, Lyketsos CG, Peskind ER, Porsteinsson AP, Mintzer JE et al. Effect of Dextromethorphan-Quinidine on Agitation in Patients With Alzheimer Disease Dementia: A Randomized Clinical Trial. JAMA. 2015, 314(12): 1242-1254.

62. Townsend M, Cleary JP, Mehta T, Hofmeister J, Lesne S et al. Orally available compound prevents deficits in memory caused by the Alzheimer amyloid-beta oligomers. Ann Neurol. 2006, 60(6): 668-676.

63. Blanchard BJ, Chen A, Rozeboom LM, Stafford KA, Weigele P et al. Efficient reversal of Alzheimer's disease fibril formation and elimination of neurotoxicity by a small molecule. Proc Natl Acad Sci U S A. 2004, 101(40): 14326-14332.

64. Wang LY, Shofer JB, Rohde K, Hart KL, Hoff DJ et al. Prazosin for the treatment of behavioral symptoms in patients with Alzheimer disease with agitation and aggression. Am J Geriatr Psychiatry. 2009, 17(9): 744-751.

65. Fraker J, Kales HC, Blazek M, Kavanagh J, Gitlin LN. The role of the occupational therapist in the management of neuropsychiatric symptoms of dementia in clinical settings. Occup Ther Health Care. 2014, 28(1): 4-20.

66. Ballard CG, O'Brien JT, Reichelt K, Perry EK. Aromatherapy as a safe and effective treatment for the management of agitation in severe dementia: the results of a double-blind, placebo-controlled trial with Melissa. J Clin Psychiatry. 2002, 63(7): 553-558.

67. Livingston G, Kelly L, Lewis-Holmes E, Baio G, Morris S et al. A systematic review of the clinical effectiveness and cost-effectiveness of sensory, psychological and behavioural interventions for managing agitation in older adults with dementia. Health Technol Assess. 2014, 18(39): 1-226.