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Identifying Better Outcome Measures to Improve Treatment of Agitation in Dementia: A Report from the EU/US/CTAD Task Force

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Abstract

For the second time in the past 3 years, the EU-US CTAD Task Force addressed challenges related to designing clinical trials for agitation in dementia, which is one of the most disruptive aspects of the condition for both patients and caregivers. Six recommendations emerged from the Task Force meeting: 1 – Operationalizing agitation criteria established by the IPA; 2 – Combining clinician- and caregiver-derived outcomes as primary outcome measures; 3 – Using global ratings to define clinically meaningful effects and power studies; 4 – Improving the accuracy of caregiver reports by better training and education of caregivers; 5 – Employing emerging technologies to collect near real-time behavioral data; and 6 – Utilizing innovative trial designs and increasing the use of biomarkers to maximize the productivity of clinical trials for neuropsychiatric symptoms.

Key words: Neuropsychiatric symptoms, agitation, dementia, Alzheimer's disease, clinical trials, NPS outcome measures.

Introduction

Agitation and other neuropsychiatric symptoms (NPS) are the most disruptive aspects of dementia for both patients and caregivers. They are associated with worse quality of life (1), greater dementia severity, earlier institutionalization, and accelerated mortality (2, 3). Despite being a major driver of high cost care (4, 5), agitation and other NPS are poorly understood and inadequately studied. In a population-based study, agitation in dementia occurred in up to 40% of community-dwelling dementia patients and 80% of patients living in nursing homes (6). Cross-sectional studies show somewhat lower prevalence estimates (7). For persons with mild cognitive impairment (MCI) the prevalence of agitation is nearly as high, according to some studies (8). There are no approved pharmacological treatments for agitation in dementia in the USA and in Europe and Canada only short-term use of risperidone is approved for severe persistent physical aggression. Several medications with conventional and novel mechanisms of action are in development.

In 2014, the International Psychogeriatric Association (IPA) published provisional consensus definition for agitation in cognitive disorders for clinical and research use. According to this definition, agitation in dementia is characterized by emotional distress associated with the presence of at least one of the following: excessive motor activity, verbal aggression, or physical aggression. These symptoms must be severe enough to cause significant impairment in interpersonal relationships, social functioning, and/or the ability to perform or participate in activities of daily living. These symptoms must not be attributable to another psychiatric disorder, environmental or medical conditions, or the physiological effects of substance use (9).

Reaching consensus on a definition of agitation in

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dementia represents an important step towards identifying new treatments since improved nosology can reduce heterogeneity in defining target conditions. These criteria need to be operationalized, so that the clinical characteristics can be aligned with what is understood about the biology and phenomenology of agitation in dementia. This will allow for the selection and assessment of measures that best capture clinically important outcomes. With this in mind, the European Union-North American Clinical Trials in Alzheimer's Disease Task Force (EU-US CTAD Task Force) focused its 2017 meeting in Boston, Massachusetts on finding the best outcome measure for agitation in dementia trials. This Task Force comprises an international collaboration of Alzheimer's disease (AD) investigators from industry and academia who meet yearly to review recent progress in developing effective treatments for AD, and reach agreement on common clinical trial approaches, while promoting collaboration and data sharing. The fact that the Task Force previously addressed some of the challenges in designing clinical trials for agitation and aggression only three years ago (10) attests to the importance of this issue.

Overview of Agitation in Dementia

Clinical presentation

In addition to the core symptoms, irritability, disinhibition, and aberrant motor activity are common. Moreover, agitation and other NPS fluctuate and overlap. For example, agitation overlaps with many other NPS, particularly depression, irritability, and anxiety, but also apathy (11). These fluctuating symptoms cluster into predictable groups with complex etiologies (12, 13). Caregivers often notice increased agitation in the late afternoon and evening, a phenomenon referred to as "sundowning" (even though it has more to do with fatigue and sensory experiences than with the sunset).

Biological mechanisms

Agitation may be due to underlying biological mechanisms or may be a consequence of delirium, environmental factors, medication, or caregiver and environmental interactions (14). Distinguishing the underlying factors that result in agitation – both biological and environmental -- is important for treatment decisions. For example, sundowning may be associated with sleep disturbances, circadian rhythm disruption, or disorientation. If associated with circadian rhythm dysfunction, this symptom may be a target for chronobiologic treatments. Moreover, the underlying biology that disrupts behavior in persons with AD interacts with short-term and long-term environmental factors, medical comorbidities, etc, due to patient vulnerability.

The neurobiological mechanisms underlying agitation in dementia may differ from those that underlie agitation in other psychiatric diseases such as schizophrenia or major depressive disorder (15). These differences likely explain the fact that drugs used to treat NPS in depression and schizophrenia seem to be less effective in dementia leading to the need for novel approaches to treatment mechanism. Notably, the US Food and Drug Administration (FDA) recently approved pimavanserin for dementia-related psychosis in Parkinson's disease, and this drug is currently in clinical trials to treat both psychosis and agitation in patients with AD and in a trial for dementia-related psychosis in multiple types of neurodegenerative disorders. Pimavanserin is a selective 5-HT2A receptor inverse agonist. If treatment responsiveness emerges across dementia causes, this could open a new window into understanding the biology and treatment of some NPS.

Neurodegeneration disrupts brain circuitry, resulting in NPS. In agitation, at least two different circuits are disrupted (15). These may be the same circuits that are disrupted in dementia-related apathy, which could explain how apathy and agitation are closely linked (16). Further understanding of how these circuits are disrupted in different patients may provide clues about patients' differential response to treatment. Assessment of circuit function might also play a role as a biomarker to assess or predict treatment response.

Agitation in dementia is also associated with alterations in the function of serotonergic, noradrenergic, cholinergic, and dopaminergic neurotransmitters, related to neurodegeneration of associated brain nuclei (17). Neurodegeneration also contributes indirectly to the emergence of NPS by making patients very vulnerable to short-term and long-term environmental factors, or medical comorbidities, and other influences, such that patients express the impact of these in their behavior. Understanding the neurophysiological factors that underlie agitation in dementia should lead to more effective treatments.

With several medications with novel mechanisms in development, a question considered by the Task Force is whether treatment development should continue to focus on phenomenology or move towards targeting neurobiologic mechanisms. A focus on phenomenology may identify those more likely to respond to a specific treatment; however, the lack of attention to the complex mechanisms and genetic and environmental factors that contribute directly and indirectly to symptoms may ultimately lead to failure to identify underlying processes that need to be targeted in order to prevent these disabling NPS. For example, both affective and executive functions impaired in agitation, suggest that multiple neural circuits are disrupted. Citalopram primarily targets the affective phenotype (18).

Available treatments

Treatment options for NPS in AD have been disappointing. Antipsychotics, anticonvulsants, benzodiazepines, and antidepressants are frequently prescribed despite little evidence of efficacy and an increased risk of adverse side effects. Citalopram, a selective serotonin reuptake inhibitor (SSRI) is one apparent success story, since clinical trials showed that this drug reduces agitation without the negative side effects associated with other SSRIs (17). Worsening cognition and cardiac side effects were observed in some patients on citalopram, potentially limiting usefulness, although these side effects might be mitigated by using the S-enantiomer of racemic citalopram (19) A subgroup analysis investigating the heterogeneity of the treatment response concluded that patients with moderate agitation and lower levels of cognitive impairment were more likely to benefit from citalopram, while those with more severe agitation and greater cognitive impairment were at higher risk of adverse responses (20).

Assessing agitation in clinical trials

Choosing the best outcome measure for clinical trials is key to treatment development for NPS. Over time, different trials have used different outcome measures, as no gold standard has previously emerged. Instruments used to assess agitation in clinical trials include broad-spectrum scales such as the Neuropsychiatric Inventory (NPI) (21) and the clinician-rated NPI-C (22), the Neurobehavioral Rating Scale (NBRS), and the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) (23); as well as agitation subscales of these instruments (NBRS, NPI, and NPI-C) or agitation-focused scales such as the Cohen-Mansfield Agitation Inventory (CMAI) (24).

The Neuropsychiatric Inventory (NPI) and its variants the NPI-Q and NPI-NH (for nursing homes), which is based on informant report, are widely used but may miss granularity as they are not designed for use as free-standing agitation instruments. The NPI-C, the clinician-rated form of the NPI (22) has a broader range that includes NPS characteristics of MCI and severe dementia, high inter-rater reliability, strong convergent validity for depression (assessed with the Cornell Scale for Depression in Dementia [CSDD]), psychosis (assessed with the Brief Psychiatric Rating Scale [BPRS]), apathy (vs. Apathy Evaluation Scale [AES]), and agitation/aggression (vs. the CMAI). The main strength of the NPI-C is that final scoring is based on experienced clinician ratings and not on subjective caregiver's input that include the so called "filter" whereby NPS reported to affect the patient reflect the caregiver's mental state instead (25). NPI-C has been translated into several languages offering advantages for international multi-site trials. Limitations of the NPI-C include its length as it has twice as many items as the NPI, and takes longer to complete, and it may be more costly as it must be administered by a skilled clinician. To date there is a lack of data concerning the agitation and aggression components of the NPI-C since this new measure has been rarely used in cohorts or trials. (Note: NPI-C was found to be feasible to use in a multi-center trial of scyllo-inositol for agitation but results have not been published).

Global scales have been widely used in clinical trials of treatments for NPS including agitation. The Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC), published in 1997 following a consensus process involving AD clinicians [26], has been modified for NPS trials (27, 28). The mADCS-CGIC uses an interview structure with worksheets to remind raters to evaluate specific NPS (e.g., depression, apathy, agitation) as well as the broader dementia. While its administration is less structured than a rating scale, this is intentional and allows the focus to be on "gestalt" of the NPS syndrome being rated. As such, it is less likely pick up trivial effects that are irrelevant to the clinical setting. In the Citalopram for Agitation in Alzheimer's Disease Study (CitAD), significant improvement compared to placebo was seen using two instruments as primary outcome measures -- the mADCS-CGIC and the NBRS-A (17).

The CMAI is agitation specific and very detailed although it historically was developed for use in nursing homes. It covers a range of clinically-relevant agitation behaviors (not symptoms) and can usually be administered in 15-20 minutes. Drawbacks include its subjective nature, since it is administered to caregivers with no clinician input, and the observation that it focuses on the assessment of many behaviors seen in advanced dementia, typically not relevant to outpatients. In addition, questions remain about what is a clinically meaningful effect size on the CMAI. In CitAD, CMAI and the NPI were used as secondary outcome measures, enabling investigators to compare these measures in terms of sensitivity to change.

Evidence for a single construct vs. symptom clusters

CMAI calculates agitation scores using a diverse group of behaviors, which are grouped into symptom clusters. Although the manual states that it is not useful to add all categories to calculate a total score since different agitated behaviors occur under different circumstances and in different people, it also indicates that behaviors may be weighted according to disruptive impact and then combined (29, 30). The long version's 29-items tend to fit models involving 3-4 factors in principal component analyses: aggressive behavior, physically non-aggressive behavior, verbally agitated behavior, and/or hiding and hoarding. The question remains of whether symptom clusters provide more clinically relevant information for clinical trials than a total score calculated by summing

all categories. Further, if a total score is used, should the factors be weighted differently? Weighting would have to be clinically determined and take into account the shape of behavioral trajectories and the clinical importance of behavioral changes.

Factor analyses from studies in different populations suggest that CMAI item scores do not cluster in a way that supports the use of factor (31). In different studies, different items "load" onto different factors and in some cases do not load at all or load on more than one factor (31, 32). If factor scores were to be used as separate endpoints, claims could be based on any one of those factors; however, this only makes sense if the different factors are independent, which is not the case. Since CMAI items as a whole represent a single construct (e.g., agitation, aggression), reflect aspects of the IPA provisional criteria, and have change scores consistent across factors (31, 32), it is most appropriate to combine them into a single total CMAI score. Separating factors may also reduce the power from the convergence of evidence across multiple domains. Change scores cluster to a greater extent than endpoint scores, and within each factor there are items that show significance while others do not, depending on the study (i.e., there is litle consistency across studies). For example, using data from a risperidone study, only change in "hitting behaviors" was significant in the physical aggression factor (33). Moreover, this study indicated that the biggest predictor of which items will show significance in treatment effects is how big the placebo effect is; thus signal-to-noise in the placebo group negatively predicts treatment effect (32).

Conclusions

To accelerate development of improved treatments for agitation, novel measures are needed to better capture behaviors that are of most concern to patients and caregivers. Operationalizing the IPA criteria is a needed first step, for diagnosis and to establish entry criteria for clinical studies. Some Task Force members advocated developing a single measure that reflects agitation as a unitary phenomenon. Since the development of new scales from whole cloth will result in additional regulatory challenges the consensus was that the best approach moving forward is to use existing datasets to construct an evidence-based single novel measure of agitation by selecting item subsets of existing scales (e.g., NPI-C or CMAI) that best reflect the IPA criteria and the situations in which agitation occurs. These data sets may include critical descriptors of setting, demographic or clinical characteristics, disease severity which could be used to improve sensitivity of outcomes for specific trials. [Recommendation #1].

The Task Force agreed that since clinician-derived and caregiver-reported assessments have overlapping strengths primary outcome measures in agitation trials should combine the two as is the case with mADCS or NPI-C, with secondary outcomes focusing on caregiver report alone, as with CMAI or NPI [Recommendation #2].

Further, global ratings should be used to define clinically meaningful effect sizes and to power studies [Recommendation #3]. This will mitigate concerns about defining meaningful benefit based on individual symptoms that are not relevant to the specific care setting. It will also streamline trials by supporting the use of smaller samples sizes and making "no-go" decisions easier.

Better engagement of caregiver-informants is critical to future treatment development [Recommendation #4]. Caregivers play an important role in the management of NPS. They not only feel the consequences of disruptive behaviors but may also be the cause of those behaviors. Giving caregivers a greater voice in management and treatment development should be coupled with efforts to improve data quality. To improve accuracy of caregiver reports it is essential to reduce the effects of inexperience and subjectivity (e.g., the caregiver "filter"). To this end, caregivers should be trained to understand what is meant by the term "agitation" and about the phenotype of individual symptoms which may provide data that is more valid and has less inherent variance.

Collection of near real-time data on agitation symptoms through briefer more frequent (e.g., daily) data collection contacts or caregiver diaries should be pursued. Technology may offer novel solutions for this objective, for example, by using digital assistants to remind people to submit assessments [Recommendation #5].

Critical improvements in clinical trial design should be implemented to ensure the provision of high quality care and to minimize placebo responses [Recommendation #6]. Trials should use systematic approaches to ensure that non-pharmacologic therapies have been considered prior to enrolling patients in medication trials (e.g, the DICE (Describe, Investigate, Create, Evaluate) approach (14)). Further, to exclude participants who do not need to be on medication, a placebo lead-in or withdrawal design should be considered. In clinical trials for severe agitation, there has been a strong bias for not selecting people who are easier to manage, although these patients may be less responsive to medication.

In the future, assessing levels of agitation or response to treatment could be improved through the use of biomarkers. The fact that agitation reflects multiple biological pathways suggests that multiple types of biomarkers – genetic, pharmacogenetic, proteomic, and performance – will be needed. In clinical and observational studies, these biomarkers will need to be validated in populations with a range of behaviors and in different settings.

Since agitation has multiple causes and mechanisms, there is no simple, single, or unique treatment. This observation demands that treatment development move towards better understanding the causes of agitation, including neurobiological factors, and the

interaction with patient factors (e.g, dementia severity, co-morbidities), and environmental factors. Since different phenotypes may reflect different types of agitation addressing causes should precede treating the symptoms. Ultimately, the field should coalesce around the development of sequential algorithms that combine "eco-psycho-social" with pharmacologic treatments for agitation, and by extension for all NPS.

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References

1. Gonzalez-Salvador MT, Arango C, Lyketsos CG, Barba AC. The stress and psychological morbidity of the Alzheimer patient caregiver. Int J Geriatr Psychiatry. 1999;14(9):701-10. PubMed PMID: 10479740.
2. Peters ME, Schwartz S, Han D, Rabins PV, Steinberg M, Tschanz JT, et al. Neuropsychiatric symptoms as predictors of progression to severe Alzheimer's dementia and death: the Cache County Dementia Progression Study. Am J Psychiatry. 2015;172(5):460-5. doi: 10.1176/appi.ajp.2014.14040480. PubMed PMID: 25585033; PubMed Central PMCID: PMCPMC4416978.
3. Okura T, Plassman BL, Steffens DC, Llewellyn DJ, Potter GG, Langa KM. Neuropsychiatric symptoms and the risk of institutionalization and death: the aging, demographics, and memory study. J Am Geriatr Soc. 2011;59(3):473-81. doi: 10.1111/j.1532-5415.2011.03314.x. PubMed PMID: 21391937; PubMed Central PMCID: PMCPMC3088883.
4. Murman DL, Chen Q, Powell MC, Kuo SB, Bradley CJ, Colenda CC. The incremental direct costs associated with behavioral symptoms in AD. Neurology. 2002;59(11):1721-9. PubMed PMID: 12473759.
5. Costa N, Wubker A, De Mauleon A, Zwakhalen SMG, Challis D, Leino-Kilpi H, et al. Costs of Care of Agitation Associated With Dementia in 8 European Countries: Results From the RightTimePlaceCare Study. J Am Med Dir Assoc. 2018;19(1):95 e1- e10. doi: 10.1016/j.jamda.2017.10.013. PubMed PMID: 29275939.
6. Steinberg M, Shao H, Zandi P, Lyketsos CG, Welsh-Bohmer KA, Norton MC, et al. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. Int J Geriatr Psychiatry. 2008;23(2):170-7. doi: 10.1002/gps.1858. PubMed PMID: 17607801; PubMed Central PMCID: PMCPMC2932652.
7. Craig D, Mirakhur A, Hart DJ, McIlroy SP, Passmore AP. A cross-sectional study of neuropsychiatric symptoms in 435 patients with Alzheimer's disease. Am J Geriatr Psychiatry. 2005;13(6):460-8. doi: 10.1176/appi.ajgp.13.6.460. PubMed PMID: 15956265.
8. Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. JAMA. 2002;288(12):1475-83. PubMed PMID: 12243634.
9. Cummings J, Mintzer J, Brodaty H, Sano M, Banerjee S, Devanand DP, et al. Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. Int Psychogeriatr. 2015;27(1):7-17. doi: 10.1017/S1041610214001963. PubMed PMID: 25311499; PubMed Central PMCID: PMCPMC4301197.
10. Soto M, Abushakra S, Cummings J, Siffert J, Robert P, Vellas B, et al. Progress in Treatment Development for Neuropsychiatric Symptoms in Alzheimer's Disease: Focus on Agitation and Aggression. A Report from the EU/US/CTAD Task Force. J Prev Alzheimers Dis. 2015;2(3):184-8. doi: 10.14283/jpad.2015.77. PubMed PMID: 26413494; PubMed Central PMCID: PMCPMC4580980.
11. Lyketsos CG, Breitner JC, Rabins PV. An evidence-based proposal for the classification of neuropsychiatric disturbance in Alzheimer's disease. Int J Geriatr Psychiatry. 2001;16(11):1037-42. PubMed PMID: 11746649.
12. Canevelli M, Adali N, Voisin T, Soto ME, Bruno G, Cesari M, et al. Behavioral and psychological subsyndromes in Alzheimer's disease using the Neuropsychiatric Inventory. Int J Geriatr Psychiatry. 2013;28(8):795-803. doi: 10.1002/gps.3904. PubMed PMID: 23147419.
13. Lanctot KL, Amatniek J, Ancoli-Israel S, Arnold SE, Ballard C, Cohen-Mansfield J, et al. Neuropsychiatric signs and symptoms of Alzheimer's disease: New treatment paradigms. Alzheimers Dement (N Y). 2017;3(3):440-9. doi: 10.1016/j.trci.2017.07.001. PubMed PMID: 29067350; PubMed Central PMCID: PMCPMC5651439.
14. 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):762-9. doi: 10.1111/jgs.12730. PubMed PMID: 24635665; PubMed Central PMCID: PMCPMC4146407.
15. Rosenberg PB, Nowrangi MA, Lyketsos CG. Neuropsychiatric symptoms in Alzheimer's disease: What might be associated brain circuits? Mol Aspects Med. 2015;43-44:25-37. doi: 10.1016/j.mam.2015.05.005. PubMed PMID: 26049034; PubMed Central PMCID: PMCPMC4600424.
16. Lyketsos CG, Sheppard JM, Steinberg M, Tschanz JA, Norton MC, Steffens DC, et al. Neuropsychiatric disturbance in Alzheimer's disease clusters into three groups: the Cache County study. Int J Geriatr Psychiatry. 2001;16(11):1043-53. PubMed PMID: 11746650.
17. Porsteinsson AP, Drye LT, Pollock BG, Devanand DP, Frangakis C, Ismail Z, et al. Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. JAMA. 2014;311(7):682-91. doi: 10.1001/jama.2014.93. PubMed PMID: 24549548; PubMed Central PMCID: PMCPMC4086818.
18. Charu V, Rosenberg PB, Schneider LS, Drye LT, Rein L, Shade D, et al. Characterizing Highly Benefited Patients in Randomized Clinical Trials. Int J Biostat. 2017;13(1). doi: 10.1515/ijb-2016-0045. PubMed PMID: 28541924.
19. Ho T, Pollock BG, Mulsant BH, Schantz O, Devanand DP, Mintzer JE, et al. R- and S-citalopram concentrations have differential effects on neuropsychiatric scores in elders with dementia and agitation. Br J Clin Pharmacol. 2016;82(3):784-92. doi: 10.1111/bcp.12997. PubMed PMID: 27145364.
20. Schneider LS, Frangakis C, Drye LT, Devanand DP, Marano CM, Mintzer J, 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. doi: 10.1176/appi.ajp.2015.15050648. PubMed PMID: 26771737.
21. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994;44(12):2308-14. PubMed PMID: 7991117.
22. de Medeiros K, Robert P, Gauthier S, Stella F, Politis A, Leoutsakos J, et al. The Neuropsychiatric Inventory-Clinician rating scale (NPI-C): reliability and validity of a revised assessment of neuropsychiatric symptoms in dementia. Int Psychogeriatr. 2010;22(6):984-94. doi: 10.1017/S1041610210000876. PubMed PMID: 20594384; PubMed Central PMCID: PMCPMC3314709.
23. Reisberg B, Borenstein J, Salob SP, Ferris SH, Franssen E, Georgotas A. Behavioral symptoms in Alzheimer's disease: phenomenology and treatment. J Clin Psychiatry. 1987;48 Suppl:9-15. PubMed PMID: 3553166.
24. Cohen-Mansfield J. Conceptualization of agitation: results based on the Cohen-Mansfield Agitation Inventory and the Agitation Behavior Mapping Instrument. Int Psychogeriatr. 1996;8 Suppl 3:309-15; discussion 51-4. PubMed PMID: 9154580.
25. Rosenberg PB, Mielke MM, Lyketsos CG. Caregiver assessment of patients' depression in Alzheimer disease: longitudinal analysis in a drug treatment study. Am J Geriatr Psychiatry. 2005;13(9):822-6. doi: 10.1176/appi.ajgp.13.9.822. PubMed PMID: 16166413.
26. Schneider LS, Olin JT, Doody RS, Clark CM, Morris JC, Reisberg B, et al. Validity and reliability of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord. 1997;11 Suppl 2:S22-32. PubMed PMID: 9236949.
27. 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. doi: 10.1097/01.JGP.0000200589.01396.6d. PubMed PMID: 16505124.
28. Sultzer DL, Davis SM, Tariot PN, Dagerman KS, Lebowitz BD, Lyketsos CG, et al. Clinical symptom responses to atypical antipsychotic medications in Alzheimer's disease: phase 1 outcomes from the CATIE-AD effectiveness trial. Am J Psychiatry. 2008;165(7):844-54. doi: 10.1176/appi.ajp.2008.07111779. PubMed PMID: 18519523; PubMed Central PMCID: PMCPMC2714365.
29. Cohen-Mansfield J. Assessment of disruptive behavior/agitation in the elderly: function, methods, and difficulties. J Geriatr Psychiatry Neurol. 1995;8(1):52-60. PubMed PMID: 7710649.
30. Cohen-Mansfield J, Marx MS, Rosenthal AS. A description of agitation in a nursing home. J Gerontol. 1989;44(3):M77-84. PubMed PMID: 2715584.
31. Rabinowitz J, Davidson M, De Deyn PP, Katz I, Brodaty H, Cohen-Mansfield J. Factor analysis of the Cohen-Mansfield Agitation Inventory in three large samples of nursing home patients with dementia and behavioral disturbance. Am J Geriatr Psychiatry. 2005;13(11):991-8. doi: 10.1176/appi.ajgp.13.11.991. PubMed PMID: 16286443.
32. Hendrix S, Brown BL, Cummings JL, Lyketsos C, Porsteinsson AP, Rosenberg PB, et al. Optimizing measurement of agitation and aggression in dementia. Alzheimer's & Dementia. 2017;13(7 supplement):P264.
33. Rabinowitz J, Katz I, De Deyn PP, Greenspan A, Brodaty H. Treating behavioral and psychological symptoms in patients with psychosis of Alzheimer's disease using risperidone. Int Psychogeriatr. 2007;19(2):227-40. doi: 10.1017/S1041610206003942. PubMed PMID: 16879763.