Rethinking Antipsychotic use in Dementia: A literature review on efficacy, safety, and alternatives

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Rethinking Antipsychotic use in Dementia: A literature review on efficacy, safety, and alternatives

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Abstract

Background and Objectives. Dementia and its associated behavioral and psychological symptoms (BPSD) significantly impact patients' quality of life, healthcare systems, and caregivers. Current treatments often include antipsychotic medications; however, their efficacy and safety profiles require careful evaluation. This review aimed to examine the use of antipsychotics in dementia, focusing on their role, efficacy, adverse effects, and clinical monitoring guidelines.

Materials and Methods. We conducted a thorough literature review in PubMed and Medline databases, using search terms like "dementia," "BPSD," "antipsychotics," "adverse effects," and "clinical guidelines." Our analysis encompassed a range of research studies, including meta-analyses, randomized controlled trials, observational studies, and clinical practice guidelines.

Results. While antipsychotics can be effective in managing severe BPSD symptoms like agitation and psychosis, their use carries an increased risk of mortality, stroke, and other adverse effects. Therefore, strict adherence to clinical guidelines and close monitoring are crucial to minimize these risks. Importantly, non-pharmacological interventions should always be the first-line treatment for BPSD whenever possible.

Conclusions. Antipsychotics may be necessary for severe BPSD when nonpharmacological approaches are insufficient. Clinicians must carefully weigh the potential benefits against significant risks, utilizing the lowest effective doses, strict monitoring protocols, and considering alternative pharmacological options when possible. Unveiling safer and more specific BPSD treatments is a critical area for continued research.

Keywords:

Dementia, Alzheimer Disease, Psychosis, Aggression, BPSD, Antipsychotics, Novel Antipsychotic, Drug interactions

Introduction

Major neurocognitive disorders, commonly referred to as dementia, are is typically marked by a persistent and ongoing deterioration in cognitive abilities and memory recall, often accompanied by a partial or severe lack of insight into deficiencies that can be severe enough to limit the capacity to perform daily tasks. Currently, it is estimated that around 47 million individuals globally are affected by dementia, and this figure is expected to escalate to 131 million by the year 2050 [1].

In addition to cognitive impairment, patients may exhibit a range of psychological and behavioral abnormalities, including disorientation, mood swings, aggression, agitation, social disengagement, self-neglect, personality changes, and communication difficulties. Physical aggression is the leading cause of emergency room visits and institutionalization. Behavioral and psychological symptoms of dementia (BPSD) can have detrimental effects on patients and their families, resulting in significant psychological and medical issues [2]. Studies have reported point prevalence rates of delusions ranging from 18% to 25%, hallucinations from 10% to 15%, and agitation or violence from 9% to 30% among patients with dementia [2]. Dementia poses a substantial burden on public health and increases the cost of care for both the patients and the general public. In the United States, the estimated annual cost of dementia care was approximately $200 billion in 2010, and globally, it was estimated to be around $600 billion [3].

Non-pharmacological interventions, such as memory training, physical exercise programs, supportive care, and social and mental stimulation, have been used to manage BPSD, including antidepressants and antipsychotics [4,5].

According to the available literature, antipsychotic prescription rates for patients with dementia range from 20% to 50%, and their use is typically reserved for severe forms of dementia associated with behavioral and psychological symptoms [5].

This literature review explores and expounds upon the function and efficacy of antipsychotic medication in the management of psychological and behavioral symptoms associated with dementia. This review includes a review of current guidelines and adverse effect profiles. The outcomes of this literature review will offer recommendations for optimizing the use of antipsychotic drugs in patient care and will inform clinical guidelines and decision-making, ultimately leading to improved health outcomes for dementia patients exhibiting behavioral symptoms such as aggression, agitation, apathy, and disinhibition.

Types of Dementia and Association with BPSD

Dementia is characterized by multiple subtypes, each with distinct features and varying degrees of association with behavioral and psychological symptoms. A research study examined BPSD occurrence across dementia subtypes in individuals residing in long-term care facilities [6].

Common BPSD symptoms across most subtypes (excluding Parkinson's disease dementia (PDD) and Dementia with Lewi bodies (DLB)) included aberrant motor behavior, agitation, and irritability. Individuals with PDD and DLB often experience hallucinations, delusions, and aberrant motor behaviors. Patients with vascular dementia (VaD) exhibit a higher risk of apathy, while those with Alzheimer's disease (AD) display a greater likelihood of aggression, anxiety, and aberrant motor behavior [7]. Frontotemporal dementia (FTD) characteristically involves apathy, disinhibition, and atypical eating patterns [8]. Individuals with unspecified dementia lack consistent BPSD patterns due to potential mixed pathologies [6].

Pathological Mechanisms of BPSD

The underlying pathogenic factors influencing BPSD include neurotransmitter imbalances, structural alterations in the brain, inflammation, neuroendocrine system dysregulation, and modifications of neurotransmitter receptors. Agitation is a particularly challenging behavioral symptom in patients with dementia, especially in those with AD, and is associated with deficits in the hippocampus, amygdala, insula, frontal cortex, anterior cingulate cortex, and posterior cingulate cortex. Studies have linked agitation and overactivity or aggression to reduced cholinergic markers in the frontal and temporal cortex as well as decreased serotonin and serotonin metabolites [9-11].

Risk Factors of BPSD

A plethora of variables impact the observable manifestations of dementia.

Comorbid Conditions:

Individuals with pre-existing neurotic tendencies or posttraumatic stress disorder may be susceptible to developing Behavioral and Psychological Symptoms of Dementia (BPSD). Moreover, the use of multiple medications, including antibiotics, antidepressants, benzodiazepines, digoxin, levetiracetam, and muscle relaxants, as well as certain other medications, can potentially exacerbate behavioral symptoms [12].

Environmental Factors

The effects of environmental factors, including a disruptive living environment and unmet patient needs, may exacerbate agitation and behavioral disturbances in individuals with dementia.

Diagnostic screening tools for BPSD

The Mini-Mental State Examination (MMSE) is a commonly used tool for screening cognitive function and identifying cognitive decline [14]. In addition to the MMSE, other assessments that can be used to screen for dementia or assess its severity include the Montreal Cognitive Assessment (MoCA), Clinical Dementia Rating (CDR), and Mini-Cog [15]. The Neuropsychiatric Inventory Questionnaire (NPI-Q) consists of 12 items and is designed to assess the various behavioral symptoms that may manifest in dementia and other neurological disorders. These symptoms include delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy, and aberrant motor activity., nighttime behavioral disturbances, and appetite [16].

Treatment Modalities for Management of BPSD

Before any specific intervention for the Behavioral and Psychological Symptoms of Dementia (BPSD) is implemented, it is essential to assess and address any discomfort experienced by patients, such as pain, constipation, urine retention, or extreme temperature and noise levels. These factors can exacerbate psychosis, and should be treated accordingly.

Non-pharmacological Treatment for BPSD

According to geriatric experts, the primary course of treatment for BPSD should be non-pharmacological therapies, which not only address psychological symptoms, but also enhance the quality of life of both patients and their caregivers.

Several non-pharmacological therapies are available, such as caregiver training. This type of training emphasizes identifying behavioral irregularities as reactions to discomfort, unmet needs, or attempts at communication. Additionally, caregivers learn to create comfortable and stimulating environments, as well as respond to patients in ways that lessen the severity of problematic behaviors (e.g., diverting attention, providing clear instructions and options, and refraining from reinforcing the behavior).

Additionally, reminiscence therapy involves patients looking back at their past through music, pictures, or conversations, while other therapies, such as massage, exercise, aromatherapy, bright light treatment to alleviate circadian disruptions, and multisensory stimulation may be employed.

Efficacy of non-pharmacological treatment

This study aimed to provide healthcare professionals with evidence-based pharmaceutical therapies for behavioral and psychological symptoms of dementia (BPSD) in the elderly population. In addition to pharmacological interventions, non-pharmacological therapies such as caregiver training have not consistently shown improvements in overall BPSD. However, some evidence suggests that massage therapy may reduce depression and music therapy may lower the overall BPSD in patients with moderate to severe dementia. Despite the potential benefits of alternative therapies, the effectiveness of these interventions remains unclear, and their use is often influenced by various factors including patient preferences, clinician experience, and resource availability. Therefore, it is essential for health care providers to remain informed about the latest research and guidelines regarding BPSD management to ensure the best possible outcomes for their patients.

Pharmacological Treatment for BPSD

A list of medications that are effective in treating BPSD is presented below.

- Antipsychotics, including both typical and novel varieties, have demonstrated effectiveness in the treatment of BPSD.
- Antidepressants, particularly Citalopram and Sertraline, have been shown to reduce agitation and aggression in dementia patients.
- The FDA and European Medicines Agency have authorized a medication containing Dextromethorphan and Quinidine, which has demonstrated some advantages in treating agitation. However, it is essential to note that this drug has also been linked to a higher risk of falls in older individuals.[18].
- Prazosin has been found to be a useful intervention for the treatment of BPSD.
- Methylphenidate may be effective in improving apathy in dementia patients.

Treatment Refractory BPSD:

Patients with treatment-resistant psychosis or acute, severe psychiatric conditions may benefit from innovative therapeutic approaches, such as transcranial direct current stimulation and repetitive transcranial magnetic stimulation. Furthermore, electroconvulsive therapy has been found to be highly effective and safe for elderly individuals, particularly in managing agitation, aggression, and depression in patients with dementia.[19].

The role of Antipsychotic Drugs in Treatment of BPSD

Off-label antipsychotics have been shown to be effective in managing severe mental events, such as aggression and agitation, in patients with BPSD despite the absence of a specific medication approved for this condition.[20].

Notably, antipsychotics are frequently administered to patients with dementia for extended periods despite the lack of evidence supporting their efficacy [21]. Individuals with dementia who reside in skilled care institutions are more likely to receive antipsychotic prescriptions than those living in the community [21].

Use of Typical Antipsychotics in BPSD

Based on current research findings, the usefulness of conventional antipsychotic medications in managing dementia patients is constrained. Haloperidol, a medication that has been authorized for the treatment of Alzheimer's disease and vascular dementia, falls under this category of drugs. Despite the potential risks and adverse effects associated with haloperidol, many medical professionals believe that it should be used with caution in patients with dementia. This medication is generally reserved for extreme circumstances and should only be used as a last resort. Thioridazine, on the other hand, is sometimes used to treat dementia patients, with the aim of reducing their anxiety symptoms. It has fewer major side effects than haloperidol [22]. However, Thioridazine was not as effective as Chlormethiazole in treating the behavioral and psychological symptoms of dementia (BPSD). Studies have suggested that Thioridazine, Etoperidone, Loxapine, and Zuclopenthixol have similar efficacies in the treatment of patients with dementia.

Use of Atypical Antipsychotics in BPSD

In accordance with available research, Risperidone, Olanzapine, and Aripiprazole hold promise for managing psychosis and aggression in individuals with Alzheimer's disease (AD) over a period of 6–12 weeks. Risperidone and Olanzapine have demonstrated efficacy in improving symptoms such as agitation and impulsiveness in patients with dementia, whereas Quetiapine has not shown any such benefits. Clinicians should make patients, their families, and caregivers aware of the potential serious adverse effects of these medications as well as the baseline cardiovascular risk associated with their use.

Mechanism of Action of Antipsychotics in Dementia.

According to a genetic study, individuals with Alzheimer's disease (AD) who possess a polymorphism in the serotonin transporter (SERT) promoter area (L/L genotype) exhibit more aggressive behaviors [24]. Additionally, polymorphisms in D1 and D3 dopamine receptors (D1R and D3R, respectively) have been linked to violence and psychosis related to dementia [25].

First-generation antipsychotics, also known as typical antipsychotics, are potent dopamine antagonists that obstruct neurotransmission. These antipsychotics are most effective when they block approximately 72% of the D2 dopamine receptors in the brain and disrupt the histaminergic, cholinergic, and noradrenergic pathways to a variable degree.

Second-generation antipsychotics, also known as atypical antipsychotics, function by blocking the serotonin receptor antagonists and D2 dopamine receptors. The most frequently involved subtype of serotonin receptor is 5-HT2A. Due to antiserotonergic antagonism, atypical antipsychotics are more effective in treating psychosis in patients with dementia [26].

Guidelines for Antipsychotic Drug Use in Dementia

The American Psychiatric Association (APA) offers recommendations for managing the behavioral and psychological symptoms of dementia, with a primary focus on the use of antipsychotic medications. The APA asserts that a comprehensive treatment plan should be created for individuals with dementia, incorporating person-centered, non-pharmacological, and pharmacological interventions.

Nonemergency antipsychotic drugs should only be administered to treat agitation or psychosis in dementia patients when their symptoms are severe, pose a threat, or cause significant distress. The APA discourages the use of Haloperidol as a first-line treatment when non-emergency antipsychotic medication is necessary and there is no indication of delirium.

The use of long-acting injectable antipsychotic drugs in individuals with dementia who exhibit agitation or psychosis is discouraged unless there is a valid reason to do so because of a co-occurring chronic psychotic disease. APA suggests initiating treatment at a low dose and gradually increasing it to the lowest tolerated dose.

Following a 4-week trial of an appropriate dosage of antipsychotic medication, if there is no evident clinical improvement, the medication should be decreased and ultimately discontinued.

Efficacy of Antipsychotics in BPSD

According to the available literature, atypical antipsychotics such as Risperidone, Olanzapine, and Aripiprazole, have demonstrated some efficacy in addressing the behavioral and psychological symptoms of dementia, including those associated with Alzheimer's disease. However, quetiapine is not been found to be particularly effective for treating these symptoms in patients with dementia. It is important to note that the use of typical antipsychotics in patients with dementia has been found to be only moderately effective, with no single medicine in this class proven superior to others. The clinical efficacy of these treatments is considered inadequate owing to the limited response to medication among many patients.

Monitoring antipsychotic treatment in BPSD

Physical Health Monitoring

The Maudsley Prescribing Guidelines recommend comprehensive monitoring for dementia patients taking antipsychotics. This includes baseline assessments and regular follow-ups at least every three months, and annually thereafter. Assessments encompass vital signs (weight, blood pressure, and pulse), an electrocardiogram (ECG), complete blood count, lipid profile, liver function tests, prolactin levels, renal function tests, electrolytes, and fasting glucose or glycated hemoglobin (HbA1c).

Review Forms Monitoring

Monitoring dementia patients receiving antipsychotics often utilizes standardized initiation and review forms. These forms, particularly the POMH-UK standards 1 to 5 audit forms, assess the medication's efficacy, side effects, and overall benefit throughout treatment. The initiation form, the first step in this process, incorporates questions on risk-benefit analysis, regular review schedules, and anticipated outcomes [28].

Adverse Risk profile of Antipsychotics in Dementia

Prescribing antipsychotics to manage psychotic symptoms and aggression in dementia patients requires meticulous consideration due to their potentially severe side effects [29]. These medications are associated with a range of risks, including pneumonia, drowsiness, unsteady walking, cognitive decline, cerebrovascular events, and even death. Specific medications carry distinct risks; for example, Risperidone and Olanzapine increase the risk of hip fractures, while Aripiprazole, Quetiapine, Risperidone, and Olanzapine may elevate the risk of acute myocardial infarction.

Numerous observational studies have indicated that there may not be any disparity in overall mortality between atypical antipsychotics. In contrast, atypical antipsychotics seem to carry a greater risk of stroke compared to conventional antipsychotics. Nevertheless, they exhibit a lower risk of all-cause death and extrapyramidal symptoms. It is crucial to recognize that regulatory bodies, including the US FDA, UK Medicines and Healthcare Products Regulatory Agency, and European Medicines Agency, have issued

cautionary statements about the use of antipsychotics in patients with dementia, given the substantial risk of fatality that is linked to their administration [31].

Adverse Effects in Elderly

The geriatric population demonstrates heightened vulnerability to the severe side effects of atypical antipsychotics, prompting recommendations against their use in older adults [32]. This susceptibility could be attributed to age-related changes in neurotransmitter levels and activity, leading to suboptimal outcomes with these medications [33]. The potential downsides include excessive drowsiness, postural hypotension (leading to increased falls), abnormal muscle movements, cognitive decline, cardiovascular complications, and adverse reactions associated with anticholinergic properties [33].

Use of novel antipsychotics for dementia

Pimavanserin, a novel antipsychotic medication, received FDA approval in 2016 for managing psychosis in Parkinson's disease. Unlike traditional antipsychotics, it exhibits high selectivity by acting as a non-dopaminergic 5-HT2A inverse agonist, meaning it primarily targets the 5-HT2A serotonin receptor. This unique mechanism of action makes Pimavanserin a promising candidate for treating BPSD [34].

Lumateperone and Brexpiprazole, a new generation of atypical antipsychotics, offer a distinct approach by targeting serotonin 5-HT2A receptors (5-HT2ARs) with minimal interaction with D2 receptors (D2Rs). These drugs act through a unique combination of partial agonism at D2Rs and 5-HT1ARs alongside antagonism at 5-HT2ARs. This unique mechanism is believed to contribute to their significantly reduced risk of extrapyramidal side effects, often associated with traditional antipsychotics, potentially due to the partial D2 receptor activation.

Lumateperone is a promising drug for treating several neuropsychiatric disorders due to its distinct mechanism of action that potentiates the activity of multiple neurotransmitter systems.[35].

Drug-Drug Interactions:

Among neuropsychiatric patients, a common drug-drug interaction (DDI) involves first-generation antipsychotics like Haloperidol and second-generation antipsychotics like Olanzapine. This combination significantly elevates the risk of extrapyramidal symptoms, a well-documented concern. Notably, research indicates that haloperidol is frequently implicated in DDIs, particularly when co-administered with Trihexyphenidyl, other antipsychotics, and Fluoxetine [36]

It is worth noting that individuals on antipsychotic therapy who smoke may require higher antipsychotic doses than those who do not. Many antipsychotics are metabolized by human cytochrome P450 (CYP) 1A2 and 2B6, which can lower plasma concentrations and reduce the efficacy of treatment in dementia patients [37].

Among all antipsychotics, olanzapine is more likely to interact with alcohol, leading to excessive central nervous system depression.

BPSD Management on Specific Disorder Level

Behavioral and psychological symptoms of dementia (BPSD) fall into five broad categories: verbal (e.g., yelling, repetitive speech), motor (e.g., pacing, physical aggression), emotional (e.g., depression, anxiety), perceptual, and vegetative (e.g., sleep and appetite disturbances) [12].

Agitation

Risperidone, Olanzapine, Quetiapine, and Aripiprazole are the primary medications used to treat agitation, and second-generation antipsychotics are the cornerstone of this approach. Additionally, Sertraline and Citalopram, two selective serotonin reuptake inhibitors (SSRIs), have been shown to effectively alleviate agitation [38]. Furthermore, Quinidine and Dextromethorphan demonstrated moderate beneficial effects on agitation.

Aggression

Verbal and physical aggression can be effectively managed using second-generation antipsychotics and selective serotonin reuptake inhibitors (SSRIs) [39]. Although Haloperidol can be used to address aggression, it may not always be effective in treating BPSD [39]. Caregiving interventions can also be useful in de-escalating problematic behaviors, including aggression [39].

Hallucination and Hostility

Second-generation antipsychotics, including Aripiprazole, Risperidone, Olanzapine, and Quetiapine, are typically recommended as first-line treatments for the management of psychosis, hallucinations, irritability, unresponsiveness, and delusions [40].

Apathy

A common symptom among individuals in the early stages of dementia is apathy, which is a non-cognitive behavioral and psychological sign. Although antipsychotics and antidepressants are sometimes prescribed to manage apathy in patients with dementia, these medications have shown little to no effectiveness. In contrast, methylphenidate, a medication with a minimal risk of side effects, may improve functionality, apathy, and cognition. A range of non-pharmacological approaches can also be effective in treating apathy, including cognitive stimulation therapy, behavioral and environmental interventions, therapeutic discourse, recall group therapy, and regular one-on-one human interactions [41].

Depression

When managing depression in patients with dementia, the combination of Citalopram and Methylphenidate has been found to have a very high response rate [1]. As first-line pharmacological treatment, selective serotonin reuptake inhibitors (SSRIs) such as Paroxetine, with minimal side effects, and Escitalopram and Citalopram, with moderate benefits, are typically prescribed [2]. Non-pharmacological management options, such as music therapy and massage therapy, have also been found to be beneficial in managing depression in patients [3, 42].

Sleep Disorders

A considerable proportion of individuals afflicted with dementia, estimated to be between 25% and 80%, have sleep disturbances that can be linked to aging and neurodegenerative disorders. To tackle these sleep-related issues, healthcare providers often resort to medicating their patients with a diverse array of prescription drugs such as Melatonin, Trazodone, Z-drugs (Zolpidem, Zopiclone, and Zaleplon), and Ramelteon. Additionally, medication regimens comprising antihistamine drugs, herbal remedies, and antidepressants like Mirtazapine [43] may also be employed.

Conclusion

Management of the behavioral and psychological symptoms of dementia is critical, as these symptoms can lead to disability and institutionalization. Non-pharmacological therapies may be useful in improving

the quality of life and reducing symptoms such as agitation, but evidence for their effectiveness is limited, except for caregiver training and music therapy. Antipsychotic drugs, including both typical and atypical antipsychotics, have been found to be weakly to moderately effective in treating psychosis and agitation in patients with dementia. However, the use of antipsychotics must be carefully considered as they can be associated with adverse effects, increased mortality, or lack of efficacy. Continuous monitoring is necessary before, during, and after treatment. Novel antipsychotic agents are being explored as potential alternatives, because they may have fewer side effects.

Conflict of Interest

The authors declare that they have no conflict of interest.

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