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REVIEW

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The role of neurotransmitter receptors in antipsychotic medication efficacy for Alzheimer's-related psychosis

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Abstract

Background Alzheimer's disease (AD) is marked by cognitive decline along with the presence of mental symptoms, most notably psychosis. Although antipsychotic drugs are commonly recommended to treat these symptoms, there is ongoing discussion on the safety and effectiveness of these drugs in AD patients. The therapeutic management of Alzheimer's disease-related psychosis (ARP) is hampered by its limited therapy options, determining the precise brain regions in Alzheimer's patients with understanding of the neurological substrates implicated in ARP. While new therapies including brexpiprazole and atypical antipsychotics present promising therapeutic choices, practical implementation and potential upcoming therapies approaches is discussed along with mechanism-based understanding of different neurotransmitters with pharmaceutical therapies. Our objective is to contribute to more efficient and individualized treatment approaches by offering a thorough resource for medical professionals and researchers working in the field of managing and researching psychosis associated with AD.

Results The examination containing new data supporting newer therapeutic approaches that target receptors and providing better safety and effectiveness characteristics. This study point out gaps in our existing understanding and make recommendations for future research, emphasizing the necessity of clinical trials created especially for psychotic Alzheimer's patients. Secondly, the neurochemical and neuropathological bases of ARP, with a focus on changes in the dopamine, serotonin, and glutamate systems of neurotransmitters are also described in detail. Different pharmacodynamics antipsychotic medications are covered in later sections of this paper, with an emphasis on how these medications' interactions with certain neurotransmitter receptors may affect their therapeutic efficacy and side-effects profile.

Conclusion The review article summarizes the most recent findings regarding the contribution of neurotransmitter receptors to the effectiveness of antipsychotic drugs in the management of ADP. We provide a thorough overview of second-generation (atypical) antipsychotics, emphasizing how their unique affinity for neurotransmitter receptors influences their clinical application in psychosis associated with AD. The difficulties of treating Alzheimer's with antipsychotics are also covered in this study, including the potential for cognitive impairment to worsen, the emergence of extrapyramidal symptoms, and other unfavorable effects. New approaches to studying and treating ARP including neuroinflammation-targeting medicines, transcranial magnetic stimulation (TMS), cerebrospinal fluid (CSF) biomarkers, and muscarinic acetylcholine receptor (mAChR) agonists like xanomeline. Reducing psychosis

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through treatment options could be improved by knowledge of N-methyl-D-aspartate glutamate receptors (NMDAR) hypofunction processes in gamma-aminobutyric acid (GABAergic) neurons.

Introduction

AD, sometimes referred to as dementia, is a debilitating neurological condition that mainly affects the elderly [1]. It causes significant cognitive impairment and steadily erodes cognitive abilities [2]. While memory loss is the most well-known indication of AD, it is not the sole manifestation [3]. Psychosis in AD covers a variety of behavioral problems, for example hallucinations, delusions, agitation, and is a significant burden on both patients and caregivers [4]. According to estimates, 50 percent or more of Alzheimer's victim may suffer from a psychotic episode while they are ill, making it a common and unavoidable feature of the disease's clinical panorama [5]. The significant effects of ARP include greater percentage of hospitalization, arrangement with healthcare facilities and faster cognitive decline in addition to an increased load and suffering for caregivers [6]. Despite their drawbacks and safety concerns, antipsychotic drugs are often used off-label in this situation and prescribing practices have become cautious due to the possibility of adverse effects, include a higher chance of stroke and death [7, 8]. Although these drugs can provide some respite from the upsetting symptoms of psychosis, there is considerable debate regarding their effectiveness in treating Alzheimer's patients [9]. Optimizing the management of ARP requires a thorough understanding of the neurological foundations of the disorder as well as the processes via which antipsychotic medicines work [10]. Considerable advancements have been achieved in comprehending complex network of neurotransmitter systems, including as the dopaminergic, glutamatergic, cholinergic, serotonergic, and gamma-aminobutyric acid (GABAergic) pathways, that play a role in psychosis by the discipline of neuropsychopharmacology. These systems are important in determining how ARP develops and are the targets of several antipsychotic drugs [11]. Cognitive neuroscience research has long been drawn to the intricate relationships between cognitive and affective processes and their underlying neural substrates. Finding the neuronal basis of these activities requires studying functional connection throughout the brain, which is the coordinating and synchronization of neural activity among different brain areas [12].

The amygdala, prefrontal cortex (PFC), and hippocampal regions are important for memory formation and learning. The amygdala, which is acknowledged for its importance in the processing of emotions, engages with the hypothalamus and other downstream structures to influence the generation of emotionally charged responses. Specific divisions and nuclei within the amygdala are among the inhibitory processes that impact memory modulation. The hippocampal area directly projects the basolateral amygdala and the infralimbic cortex in the PFC, which is important for spatial navigation and contextual memory and the fact that different hippocampal subregions have been connected to a variety of human behavioral characteristics highlights the varied functions that these regions play in cognitive processes [13]. In addition to exercising top-down management of emotional responses, the PFC is essential to cognitive functions related to the extinction of fear memories. The PFC and amygdala must cooperate within the framework of working neural pathways for adaptive fear management to occur [12], the degree of delusions was found to be negatively correlated with the right hippocampus volume and middle frontal gyrus volume in bilateral frontal, parietal, and striatal areas. Additional research indicates that in people with AD and delusions, the left inferior parietal lobule shows less functional connection than the frontal areas [14].

Alzheimer's disease and psychosis

AD, common neurodegenerative ailment, possesses a steady decline in cognitive ability [15]. The aging population and the healthcare institutions that support them face enormous challenges as a result [16]. Apart from prominent sign, memory loss, AD involves a range of neuropsychiatric manifestations [17]. Psychosis in AD is among the most upsetting as well as challenging features of the condition among these [18]. A chronic and more crippling neurodegenerative illness [19], AD remains typified by the subtle deterioration of memory and cognitive function [20]. Its characteristic pathology is the build-up of tau tangles and beta-amyloid plaques in the brain, which cause synaptic dysfunction and neuronal death [21]. As the global population ages, prevalence of AD has increased dramatically, placing a significant strain on healthcare institutions and society at large [22] (Fig. 1).

Psychosis in Alzheimer's types and impact

Alzheimer's-related psychosis (ARP), which is psychosis within the framework of AD, range of disconcerting neuropsychiatric symptoms that have a significant impact on both the diseased person and their caregivers [24]. The two most prevalent forms of psychosis in AD are misbeliefs, which are firmly believed to be

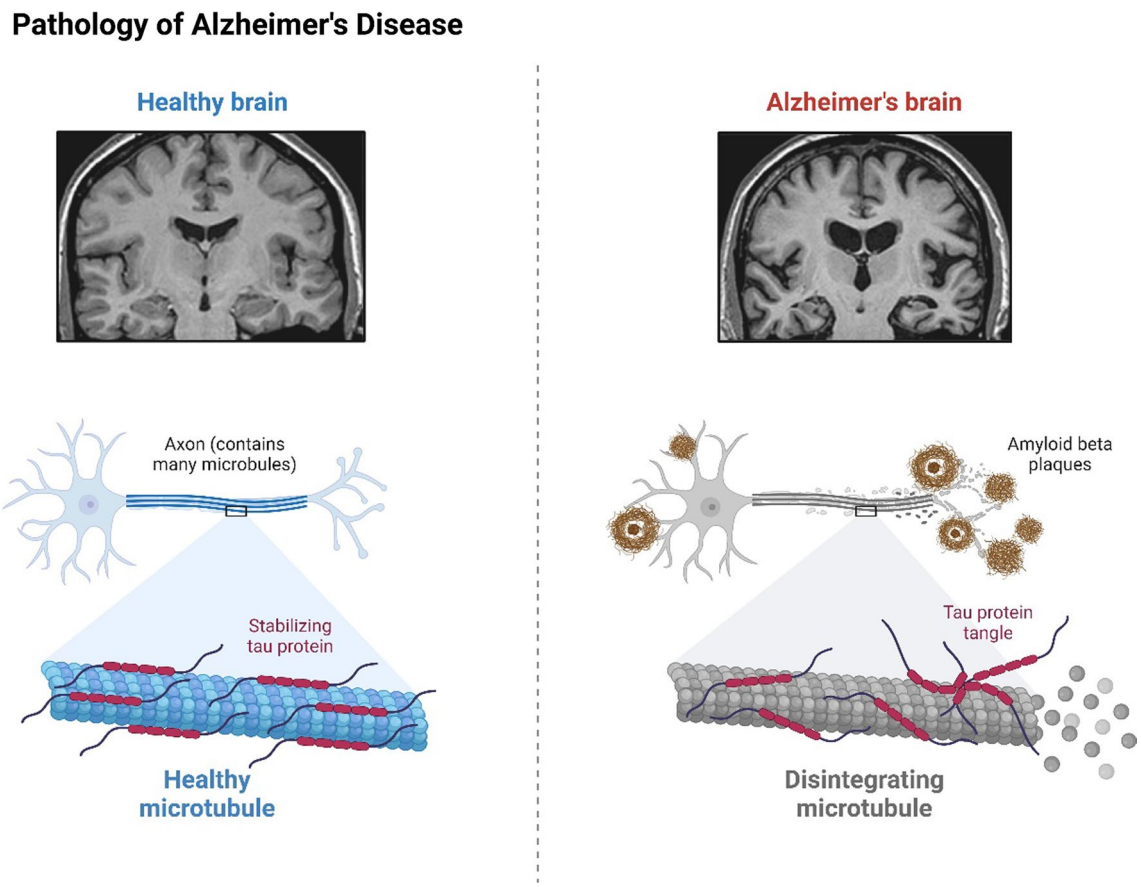


Fig. 1 Comparing the pathological characteristics of the healthy brain with the brain affected by AD [23]

untrue ideas that can vary from paranoia to grandiosity, and hallucinations, which are sensory experiences that have no basis in reality [25]. ARP has a significant emotional and practical impact that exacerbates the significant difficulties that come with cognitive loss. People who have ARP have increased emotional upheaval and discomfort, and those who care for them must manage these symptoms while also making sure their loved ones are safe [26]. Beyond just emotional problems, ARP causes more hospital stays, placements in nursing homes, and a faster rate of cognitive deterioration [27]. These comorbidities may also be influenced by synaptic dysfunction, atrophy in specific areas of the brain and the degeneration of neural tissue. Moreover, chemicals that promote inflammation substances such interleukins and tumor necrosis factors can cause inflammatory disruptions, which are categorized as possible hazard issues in various psychotic indications in patients with AD. It is critical to carry out carefully planned trials to look into both medicinal and non-medical therapies that is able to enhance the method of caring for these individuals because there is less information available regarding the possible management choices [24] (Fig. 2).

Challenges in diagnosis and assessment

The cognitive impairments associated with Alzheimer's disease pose special obstacles for diagnosing and evaluating ARP because they can impair patient's ability to accurately self-report and caregivers capacity to give in-depth accounts of psychotic experiences [28]. One diagnostic challenge is differentiating ARP from other sources of psychosis, like delirium or other mental illnesses [29]. A thorough examination requires objective evaluations, such as neuropsychological testing, neuroimaging, and biomarker analysis, which can be resource-intensive [30] and may not always be available in the context of the medical profession [31]. To ensure a precise and efficient treatment of ARP, navigating these difficulties is essential. An important role for dopaminergic dysregulation, which has historically been linked to schizophrenia, is becoming apparent in ARP [32].

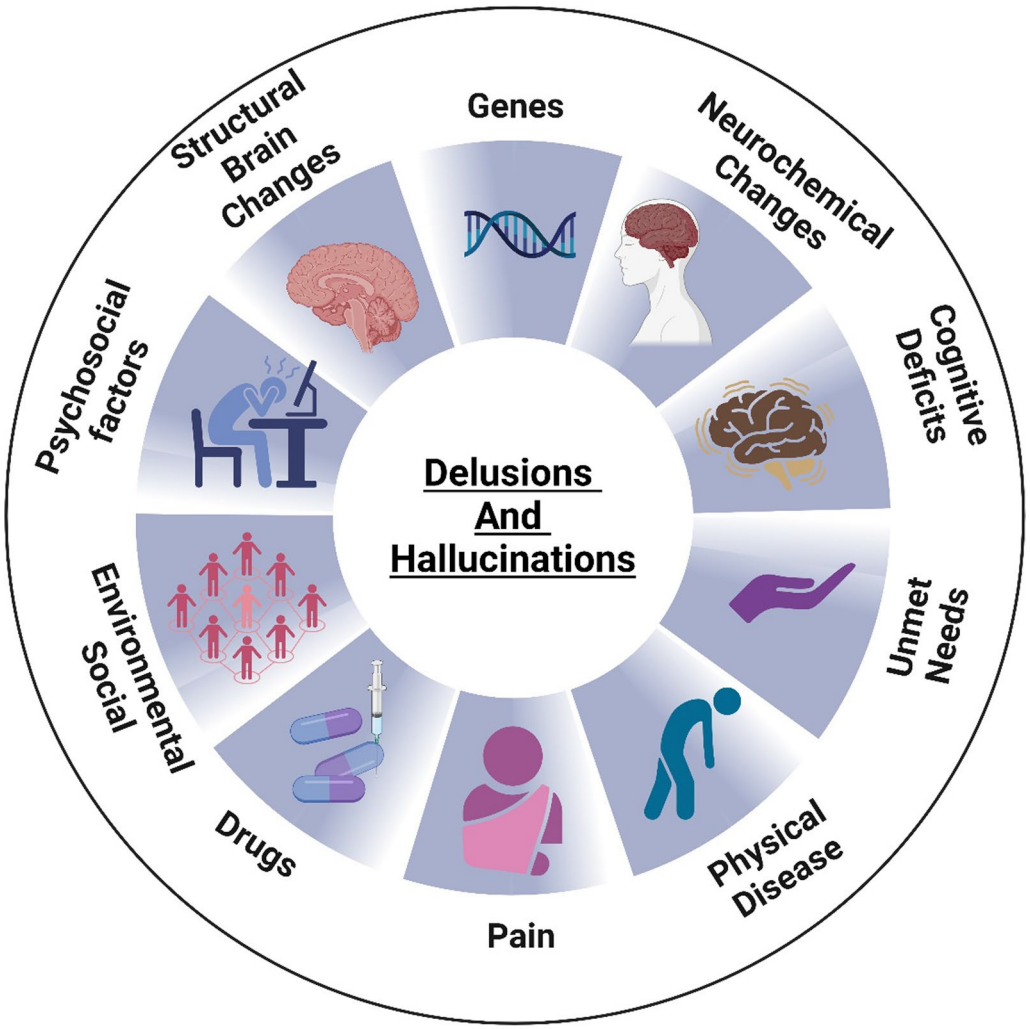


Fig. 2 Factors affecting dementia patients' psychotic symptoms

Mechanism-based understanding

Neurotransmitters

Dopamine

Among Alzheimer's disease individual experiencing psychosis, there is a rise in dopamine 3 receptors (D3R) density in the nucleus accumbens [33]. Psychotic AD has been linked to changes in the expression of the striatal D3R, whereas a therapeutic window for treatment response is determined by the presence of antipsychotics in the striatal D2R modifications. Some of the central nervous system stimulants such as methylphenidate exposure (both acute and long-term) can cause increases in extracellular dopamine brought on by drugs to lead to psychosis and cocaine with the levodopa-induced iatrogenic psychosis associated with Parkinson illness [34]. Remarkably, there is no proof that the usage of dopaminergic psychostimulants in AD leads to a higher risk of psychotic symptoms while treating behavioral disorders [35]. A PET (positron emission tomography) investigation on 21 AD patients utilizing (11C) raclopride revealed that AD patients with delusions have more striatal dopamine (D2/D3) receptors than AD patients without delusions and higher levels of striatal D2 receptors are linked to wandering and delusional thoughts [36] (Fig. 3).

Serotonin

Psychosis in AD patients has also been linked to changes in the serotonergic system. Post-mortem and imaging

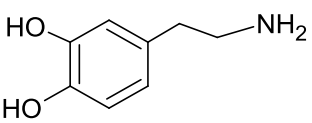


Fig. 3 Dopamine

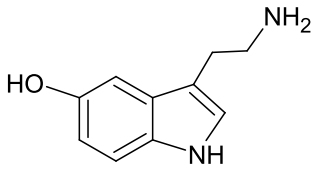


Fig. 4 Serotonin

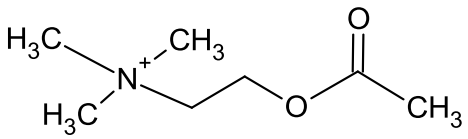


Fig. 5 Acetylcholine

investigations suggest that 5-hydroxytryptamine 2A receptor (5HT2A) is probably a major receptor target for antipsychotic activity [37].The pathogenesis of AD-related psychosis is likely to include serotonin receptors, particularly 5-HT2A [38]. Atypical antipsychotic activity is refined by pimavanserin, an extremely selective inverse agonist of the 5HT2A receptor that links on the receptor but produces an opposing effect as an agonist. This could be significant advancement in the management of AD psychosis. It has recently received Food and Drug Administration approval in the United States to manage psychotic associated with Parkinson illness [37] and recently, a phase II randomized controlled trial (RCT) with 181 AD patients who had psychosis was concluded, and the top line results were favorable [39] (Fig. 4).

Acetylcholine

For psychotic symptoms in certain illnesses, cholinesterase inhibitors, or ChEIs, may be a helpful medication. A literature review of data suggests that treating people with AD with ChEIs improves psychotic symptoms. A phase II RCT of 181 participants with AD psychosis was just finished, and the top line results were encouraging. In Ref. [40]. Anticholinergic drugs cause mental state alterations that resemble the AD symptoms related to neuropsychiatry, such as disarray in thinking, visual hallucinations, and fluctuations in mood. Individuals experiencing AD are remarkably susceptible to the negative consequences of anticholinergic substances. Acetylcholinesterase inhibitor-treated patients with neurologic illnesses and concurrent has shown that cholinergic deficiencies reduce neurological signs. Acetylcholinesterase inhibitor therapy improves behavioral symptoms in Lewy body dementia patients. Similarly, individuals with dementia and Parkinson disease who also experience delusions and hallucinations may find neuropsychiatric relief from angiotensin-converting enzyme (ACE) inhibitor treatment [41] (Fig. 5).

Cholinergic muscarinic receptors

The acetylcholine neurotransmitter system cholinergic muscarinic receptors have been connected to psychosis neurobiological [42]. An M1/M4-preferring muscarinic acetylcholine receptor agonist with surprising antipsychotic effect was created to treat cognitive sign of AD [43], also these M1 and M4 agonist, dramatically and dose-dependently decreased AD patients agitation and psychosis [37]. The cholinergic system is a neuromodulatory system that is widely distributed and its sources include acetylcholine which is produced and released by cholinergic projection neurons from two different groups: the brainstem centers, that stimulate the midbrain, hindbrain, thalamic, and cerebellar areas, and the basal forebrain cores, which stimulate cortical, hippocampal, and regions of the thalamus. A potential benefit of cholinergic stimulation is that it can alleviate cognitive dysfunction or psychosis in brain disorders like AD or disorders related to the nervous system [44]. In addition, elevated muscarinic receptor binding has been seen in the cortices of AD sufferers experiencing psychosis. Unlike dopaminergic therapies, anticholinergic medication use has been linked to psychosis in AD, with exposure more than doubling the chance of incident psychosis. Psychosis in AD is thought to be related to abnormalities in cholinergic neurotransmission. It has been demonstrated that cholinesterase inhibitors, which are used in the cognitive therapy of AD, reduce the onset of psychotic symptoms. Since the microtubule-associated protein tau (MAPT) gene has no known autosomal dominant mutations linked to familial AD, tau pathology in the brain has been thoroughly documented and has been shown to have transdiagnostic significance to psychosis, including in AD (35). Particularly, it has been discovered that gene polymorphisms in the M1 receptor (CHRM1), the M4 receptor (CHRM4), and the M2 receptor (CHRM2) in patients with schizophrenia who are taking high doses of antipsychotics are linked to psychiatric symptoms and cognitive function in schizophrenic patients [45].

Genetic studies

Significant progress has been made in recent years in determining the genetic correlates of psychosis [P] in AD [46] and recent data indicate that the strongest correlation between AD and psychosis and genetic susceptibility to schizophrenia occurs when the research is limited to people who have delusions [47] pointing to share delusional pathways as a key component of psychosis in all age groups [46]. The first single nucleotide polymorphism [SNP]-based genome-wide association study (GWAS) to assess the heritability of psychosis in AD was published in 2021 and involved

over 12,000 individuals with AD. Two loci in SUMF1 and ENPP6 were found to have strong genome-wide correlations with AD + P. The only one to reach the threshold for genome-wide significance was apolipoprotein E (APOE) ($p = 1.23 \times 10 - 6$) in gene-based analysis. The APOE risk haplotype ε4 was found to have a strong correlation with APOE by gene-based research. AD + P showed a positive genetic link with depressed symptoms and a negative genetic correlation with cognitive and educational performance [48]. There is inconsistent evidence linking a number of additional genes, primarily associated with schizophrenia (SCZ), to the presence of psychosis in AD. In reality, the concept that a complex genetic basis may underlie this symptom is supported by the strong relationships that Numerous SNPs, which include the APOE gene, have been linked to psychotic disorders in Alzheimer's disease, according to GWAS [49] (Fig. 6).

Pharmacological intervention

Atypical antipsychotics

Atypical antipsychotics have drawn attention in the management of psychosis in Alzheimer's patients because of their possible advantages and disadvantages [50]. Some of the atypical antipsychotics such as, risperidone, olanzapine, quetiapine and aripiprazole may be useful for extremely agitated, aggressiveness, and psychosis connected to Alzheimer's disease. Their mechanism of action involves the antagonism of dopamine and serotonin receptors, which offers therapeutic advantages over traditional antipsychotics, another such benefit is a decreased likelihood of additional symptoms. Nonetheless, there are some serious issues with their use [51]. Research has outlined a number of risk factors for the onset of psychotic signs in Alzheimer's patients. The ones that are brought up most often are: advanced age, gender, psychiatric history, low educational background, degree of cognitive deterioration and its impact on daily functioning, lengthy history of dementia, and institutionalization [52]. Antipsychotic medicine is the recommended

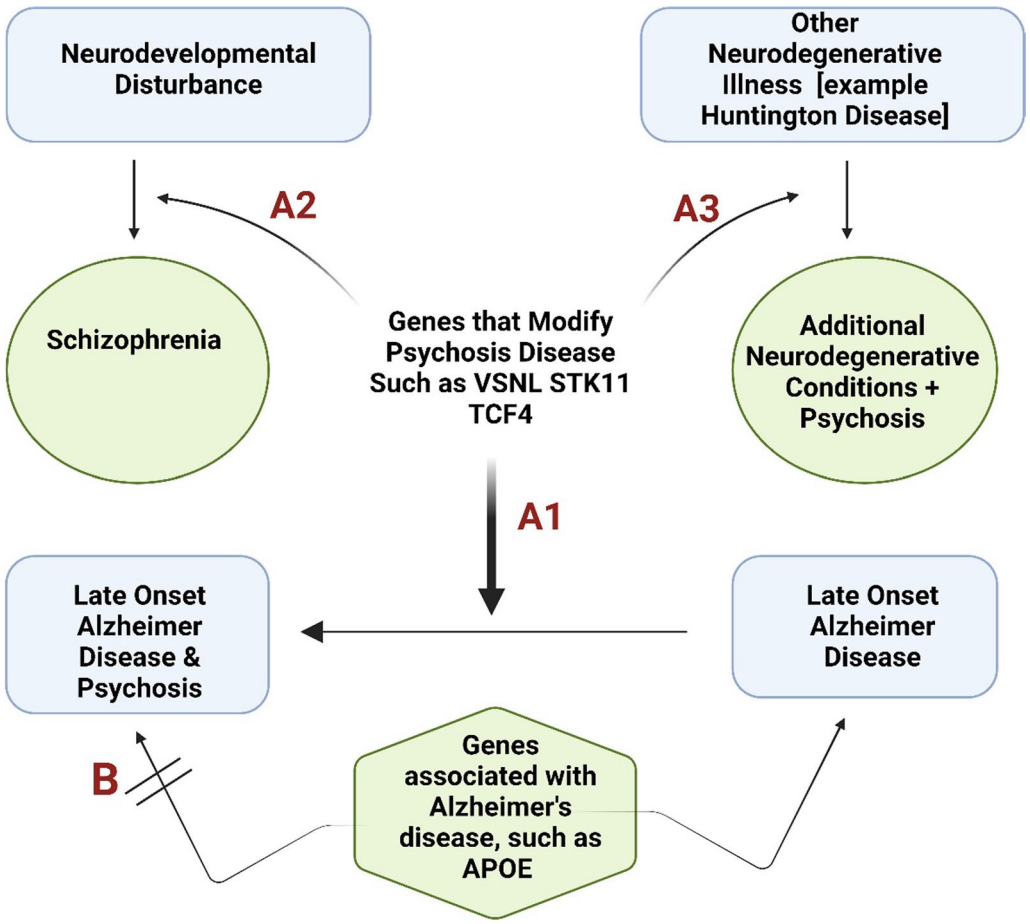


Fig. 6 A genetically based model of psychosis and Alzheimer's disease

treatment option among the numerous pharmacological alternatives for psychotic symptoms and non-pharmacological therapy approaches, such psycho-social therapies, have minimal effect on psychotic symptoms but can be helpful in improving behavioral symptoms and mood disorders like depression symptoms [53]. Numerous research endeavors have focused on examining the effectiveness and safety record of antipsychotics in managing dementia-related symptoms of psychosis, specifically AD [52]. Only risperidone is recommended for psychosis and agitation in dementia patients in the European Union and Canada, whereas no drugs are permitted for these conditions in the USA. Cerebrovascular accidents, extrapyramidal symptoms (EPS), falls, and mortality are among the risks caused from these medications. Compared to second-generation [also known as atypical] antipsychotics, the hazards appear to be higher with older antipsychotic medications [54]. The Food and Drug Administration (FDA) black box warning for these medications emphasizes a higher elderly dementia patients risk of stroke and death, though CL psychiatrist may use these medications sparingly to treat the neuropsychologic symptoms of dementia in a hospital setting, such as psychosis and hallucinations. Although the higher risk is assumed to be brought on by infectious and cardiovascular problems connected to antipsychotic medication use, this is not entirely understood [55] (Table 1).

Emerging pharmacological treatments

There has been a little but positive growth in the quantity of chemicals undergoing trials in latest years. Citalopram and pimavanserin were identified as the two utmost auspicious possible treatments in the most recent Delphi consensus [57].

Pimavanserin

Pimavanserin is currently being investigated in patients with AD psychosis, having been approved by the FDA to treat Parkinson disease (PD) psychosis. It is an atypical antipsychotic which does not bind to histamine, dopamine, or muscarinic receptors, as it is a highly selective 5-HT2A inverse agonist. [58]. It is given orally at a daily dose of 34 mg (as two 17 mg tablets) without titration and shows the most frequent side effects, including peripheral edema, falls, agitation, and aggression [59].

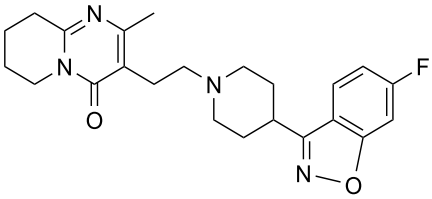
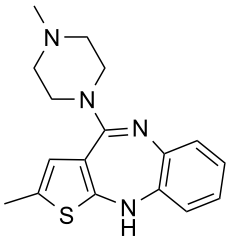
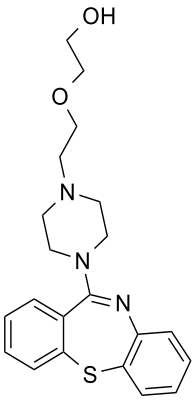
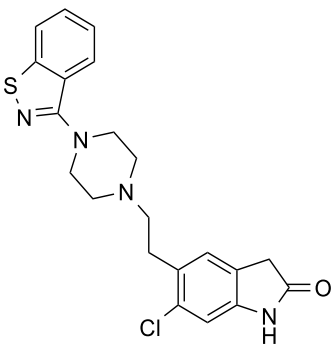
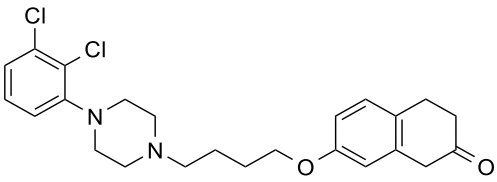
During a phase II trial with patients from AD nursing homes shown moderate efficacy at the 6-week (a priori end point) in terms of a reduction in psychosis scores on the nursing home version of the Neuropsychiatric Inventory (NPI) [Cohens d effect size 0.32 for Pimavanserin over placebo] [60] and a post hoc analysis showed that the medicine had a significantly larger treatment impact than placebo among participants with more severe psychosis [effect size of 0.73]. Additionally, 88.9% of the pimavanserin-treated group had a psychosis score reduction of ≥ 30%, while 43.3% of the placebo group had the same reduction [61]. In another study participants with all-cause dementia were recruited for a phase III relapse prevention research [62]. Those who responded to Pimavanserin underwent a 6-month double-blind withdrawal period (62% of those on open-label medication). The study was stopped at the predetermined intermediate analysis because the drug-treated group had 2.8 times fewer psychotic relapses than the placebo group [63] (Fig. 7).

Citalopram

It has been demonstrated that citalopram reduces agitation in Alzheimer's patients and researchers assessed whether citalopram medication improved additional neuropsychiatric symptoms in comparison to placebo [64]. Citalopram, selective serotonin reuptake inhibitors (SSRI), is commonly used in elderly people [65] and it has been proposed as a treatment option for dementia agitation and violence in place of antipsychotic medications [66]. Citalopram (10–30 mg/day) used orally for three weeks reduced AD-related agitation in a way that was clinically significant. It is therefore advised that clinical trials be carried out to evaluate citalopram at lower dosages (less than 30 mg/day). Heart-related adverse effects and modest cognitive loss have been linked to citalopram [67]. It also has the potential to lengthen the QT interval on an ECG, raising the possibility of irregular cardiac rhythms, which may cause risk to elderly people [68].

A multicentered, randomized, placebo-controlled, double-blinded, parallel-group trial was conducted by researchers called as Citalopram for Agitation in Alzheimer's Disease Study (CitAD) (NCT00898807). In this trials the individuals with clinically severe agitation and likely AD, were treated with citalopram and compared in conjunction with a standardized practical psychosocial intervention; a sedative component has been shown to reduce agitation. Furthermore, in week nine, Citalopram has shown promise in treating hallucinations; yet, a placebo has shown to be preferable in treating sleep difficulties and the fact that Citalopram (30 mg/day) has been linked to a notable rise in QTc interval in these patients is crucial to take into account [69]. A review of the genetic correlates of treatment response in a sub-study revealed a connection between Citalopram responsiveness and polymorphisms of the 5-Hydroxytryptamine Receptor 2A (HTR2A) and 5-hydroxytryptamine receptor 2C (HTR2C) receptors, indicating a potential mechanism for the treatment of agitation. However, no such analysis included psychosis [5] (Fig. 8).

Table 1 Molecular structures and side effects of atypical antipsychotic medications

Atypical antipsychotic	Molecular structure	Side effects
Risperidone		Heightened risk of ejaculatory dysfunction, weight gain, metabolic abnormalities (such as diabetes), increased risk of cerebrovascular events, and extrapyramidal symptoms
Olanzapine		Significant rise in body weight, altered metabolism, sedation, and risk of cerebrovascular accidents
Quetiapine		Reduced chance of extrapyramidal symptoms, but may result in orthostatic hypotension, sedation, and altered metabolism
Ziprasidone		Heart rhythm problems (QT prolongation), reduced body weight, and extrapyramidal symptoms
Aripiprazole		Less likely than others to have metabolic side effects, but can still result in akathisia, anxiety, and insomnia[56]

New atypical antipsychotics

Brexpiprazole is a new third-generation antipsychotic that acts as an antagonist at noradrenaline α1B/α2C receptors, a partial agonist at the serotonin 5-hydroxytryptamine receptor (5-HT) 1A receptor (R) (5-HT1AR), a partial agonist at the dopamine D2 receptor, and an antagonist at the serotonin 5-HT2A/5-HT2B receptor but unlike other atypical antipsychotics this

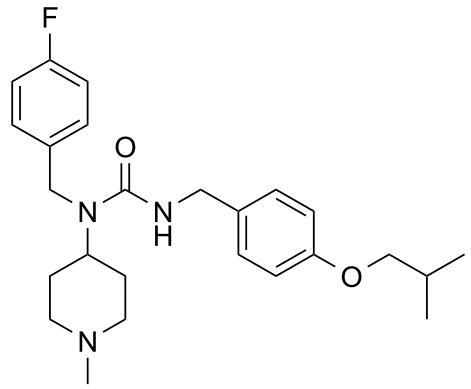


Fig. 7 Pimavanserin

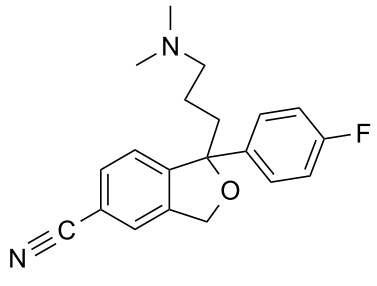


Fig. 8 Citalopram

intermediate level aims to stay below the threshold where good sensations brought on by high dopamine development grow, without going too low, preferably to prevent negative consequences like extrapyramidal symptoms (EPS) [70]. The FDA has just approved brexpiprazole for the treatment of schizophrenia and major depressive disorder as an adjuvant to antidepressant medication where akathisia and weight gain were the most often reported side effects associated with therapy.

Brexpiprazole is administered orally once [71] and it is interesting to note that brexpiprazole 2 mg/day has the potential to be an effective, safe, and well-tolerated medication for agitation in individuals with AD, according to two separate phase III clinical trials that included a total of almost 700 adult participants with AD in 2019[72]. Brexpiprazole is hypothesized to have depressive effects due to its significant affinity for inhibiting 5-HT2C-R and 5-HT7-R, blocking 5-HT2C-R probably raises frontocortical norepinephrine and dopamine in a manner similar to that of the antidepressant mirtazapine. 5-HT7-R antagonistic effects, such as those seen in the antidepressant effects of vortioxetine and lurasidone, probably enhance cognition and circadian function. It also exhibits a substantial affinity for 5-HT2A-R Antagonism, which reduces extrapyramidal symptoms (EPS) by enabling higher concentrations of DA to work in the nigrostriatal system [73].

A new FDA-approved drug called lumateperone is used to treat schizophrenia based on a mechanistic approach [74]. It is a novel medication that selectively and simultaneously modifies glutamate, dopamine, and serotonin. Lumateperone is also in phase III clinical for the treatment of bipolar depression and agitation linked to dementia, especially AD, it is also in the approval process for schizophrenia [75]. This medication is effective in treating both positive and negative in addition to cognitive decline, in schizophrenia, with a 60-fold greater affinity for 5-HT2A receptors than D2 receptors, Lumateperone is a high-affinity 5-HT2A receptor antagonist. When the dosage is increased, it acts as a mesolimbic and mesocortical selective post-synaptic antagonist and presynaptic partial agonist at D2 receptors. Furthermore, in a mesolimbic-specific way, lumateperone phosphorylates glutamatergic N-methyl-D-aspartate glutamate receptors (NMDA) GluN2B receptors and inhibits the serotonin transporter [76]. It is considerably less likely than many other atypical antipsychotic medications to result in side effects such as dry mouth, constipation, weariness, insomnia, and drowsiness when sleeping, in addition, the majority-mild side effects of Lumateperone were drowsiness, somnolence, weariness, and constipation which occurred at a clinically significant rate [77]. The dose-dependent clinical impact profile of lumateperone suggests that the medication may have a broader therapeutic range, when used in small dosages, lumateperone has sedative and anti-aggressive properties, and it may be able to accomplish these effects at low doses because it lacks D2 receptor binding and has substantial selective 5HT2A antagonist activity at low concentrations. Raising the doses is necessary to increase the number of D2 receptors, their occupancy, and the affinity and 5HT2A receptor occupancy [78]. Oral administration of the medication in the form of capsules is recommended at a dose of 42 mg. For optimal effectiveness, it is best taken after a full night sleep, and a daily dosage of 120 mg has not been shown to have any statistically significant impact on the result [75]. When used orally, it takes 13 to 21 h to be absorbed and the T-max starts to show results three to four hours after the regimen starts [78]. Lumateperone and its metabolites are hardly ever eliminated by the kidneys or urinary system, some lumateperone users have a range of side effects, from minor to serious [76]. The cytochrome (CY) P450-3A4 isoenzyme metabolizes lumateperone, and it interacts with both its stimulators and inhibitors, if a patient is taking medicine that inhibits or activates CYP3A4, they should not use lumateperone. Even though this medication also has

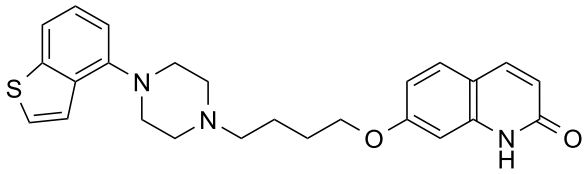


Fig. 9 Brexpiprazole

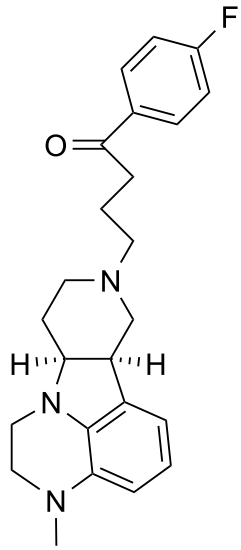


Fig. 10 Lumateperone

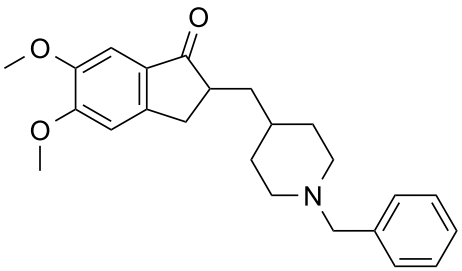


Fig. 11 Donepezil

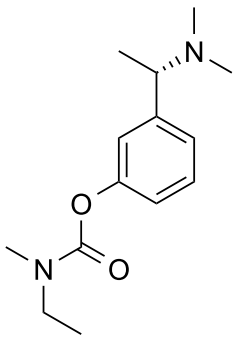


Fig. 12 Rivastigmine

a sedative effect, it probably would not work well with other sedatives like alcohol [79] (Figs. 9, 10).

Anti-dementia

Managing psychosis in AD is a difficult task, and using anti-dementia medications in this situation calls for cautious thought [80]. NMDA receptor antagonists memantine, with a maximum oral dosage of 20 mg per day and potential side effects involve headache, nausea, diarrhea, or dizziness [81] and cholinesterase inhibitors (rivastigmine and galantamine) are two anti-dementia medications that are mostly used to alleviate the cognitive symptoms of AD [82]. In which the therapeutic dosage of Rivastigmine delivered by transdermal patch ranges from 4.6 mg to 13.3 mg per 24 h in clinical practice, and the suggested initial dosage of rivastigmine in the form of liquid or pill forms is 1.5 mg twice daily, displaying side symptoms like nausea, vomiting, weight loss, tremors, diarrhea, and disorientation [83]. There are two forms of galantamine that are available: extended-release capsules and tablets with instant release. The recommended dosage for each formulation is 5 mg or 10 mg, to be taken once daily for a duration of 24 weeks [83]. The drug may cause gastrointestinal side effects such as nausea, vomiting, diarrhea, and loss of appetite when starting treatment, and these side effects may worsen when the dosage is increased. Additionally, the drug's cholinergic effects may cause urinary retention and sinus bradycardia [84]. Although cholinesterase inhibitors have a well-established track record in treating cognitive symptoms in AD, it is unknown whether or not these drugs can be therapeutically helpful in treating AD psychosis, and no randomized controlled trials have been done in this regard. However, cholinesterase inhibitor use was associated in the AD subgroup with a decreased chance of starting antipsychotics, according to an analysis from the Swedish Dementia Registry [76]. There is no direct RCT evidence demonstrating a specific advantage in the treatment of clinically severe AD psychosis, despite the fact that donepezil, with highest daily dosage of 23 mg once daily, contributing to diarrhea, nausea, vomiting, vagotonic effects (bradycardia, heart block, syncope), tremor, insomnia, urinary incontinence, and seizure [83] and memantine have been shown to diminish the onset of psychosis in AD [5]. These observations are compatible with the cholinergic pathways reported in AD psychosis, even if this observation does not support a treatment benefit. They may also point to a potential substitute for onerous psychiatric medicines in the management of non-psychotic seizures. Once more, prospective trials are necessary [85] (Figs. 11, 12, 13 and 14).

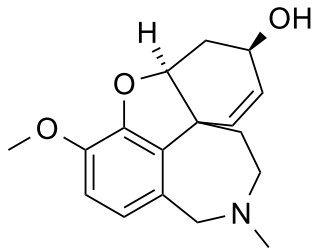


Fig. 13 Galantamine

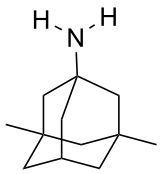


Fig. 14 Memantine

Vitamin D

Scholars are starting to utilize the correlation between insufficient vitamin D and neurodegenerative illnesses to investigate the potential involvement of vitamin D deficiency in AD psychosis. People with AD or mild cognitive impairment (MCI) who did not experience psychosis were found to utilize vitamin D more frequently, and this use was also associated with a delayed onset of psychosis.[86]. Six of the nine case–control studies found lower serum concentrations of 25-hydroxyvitamin D, a metabolite of vitamin D3, suggesting substantial differences between the AD cases and control groups. As a result, insufficient vitamin D is thought to be a risk factor for AD. On the other hand, vitamin D protective impact against AD + P was recently found, and its mechanism may offer a novel approach to treating and preventing AD + P. Vitamin D can have its protective impact by reducing the oxidative and nitrosative damage caused by high levels of nitric oxide (NO) and Inducible nitric oxide synthase (iNOS) in nerve cells [85]. Additionally, data point to a possible connection between vitamin D pathway abnormalities and amyloid pathology, which helps to explain vitamin D protective function in AD [87].

Risk assessment strategies, monitoring protocols, and mitigation strategies

It is critical to perform a comprehensive risk assessment taking into account health history, pharmaceutical history, and cardiovascular risk factors while utilizing antipsychotic drugs to manage psychosis. Baseline evaluations and routine monitoring of mental symptoms, cognitive performance, vital signs, and metabolic indicators should be part of monitoring regimens. Monitoring anthropometric measurements and body compositions (weight, body mass index (BMI), waist circumference (WC), blood pressure (BP), fasting plasma glucose (HbA1c), and lipid profile are among the factors that are advised to be observed [88].

Starting with low dosages, choosing drugs with manageable side effects, and taking into account complementary therapies are all examples of mitigation techniques [89].

Future directions in the treatment of psychosis-related Alzheimer's disease

Over the past ten years, there have been notable developments in the clinical assessment and management of psychosis and other neuropsychiatric symptoms in dementia. One of these turning points was when antipsychotic prescriptions decreased as a result of the high danger connected with these medications [90]. Aripiprazole, risperidone, amisulpride, and escitalopram are examples of drugs that have been improved for safer precision-based treatment. Other measures that have led to the development of safer, more effective treatments include the development of a clinical trial program for pimavanserin and a strong focus on non-pharmacological interventions like DICE (describe, investigate, create and evaluate) or WHELD (Well-being and Health for People with Dementia) [40]. Studying dynamic changes in receptor activity might shed light on how a treatment is working through neuroimaging techniques like fMRI (functional magnetic resonance imaging) and PET [91]. The best time to start treatment may be determined by longitudinal research monitoring the development of neurotransmitter receptor alterations during Alzheimer's-related psychosis [92]. The creation of The Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART) psychosis and MBI criteria, as well as the advancement of the IPA (International Psychogeriatric Association) psychosis criteria, should support this endeavor. In fact, these objectives were specifically considered when developing the ISTAART psychosis criteria. These criteria, which frame psychotic symptoms, place late-life emergent psychosis on a spectrum and consider cognitive stages, symptom modality, natural history of symptoms, and biomarkers associated with AD [93]. Frameworks for cross-sectional and longitudinal research could be used to improve our understanding of the clinical, cognitive, and neurobiological aspects of AD psychosis, as well as to support the creation and application of non-pharmacological therapies and medication discovery and repurposing [6]. Also, multiple connections between processes affecting synaptic function and psychosis in AD have been found using functional genomic and post-mortem

data findings [49]. The potential of therapies that target neuroinflammation, such as immunomodulators or anti-inflammatory medications, to lessen the symptoms of psychosis in AD is currently being investigated [94]. A non-invasive treatment method called transcranial magnetic stimulation (TMS) stimulates underlying nerve cells by altering the magnetic field. Research is being done on TMS as a potential treatment for dementia and other neurological conditions [95]. The cerebrospinal fluid (CSF) biomarkers play a significant role in the diagnostic process when it comes to identifying AD and other dementia in older individuals who exhibit psychotic symptoms [96]. The muscarinic acetylcholine receptor (mAChR) agonist xanomeline has been shown to reduce psychotic symptoms and enhance cognition in Alzheimer's disease patients and can be targeted as a new approach to potentially treat psychotic disorders [97]. Early postnatal GABAergic neurons experience NMDAR hypofunction, and there is considerable variation in the processes underlying this phenomenon. It would be beneficial to reduce psychotic symptoms if future study could identify the upstream and downstream mechanisms of NMDAR hypofunction [98]. In conclusion, prioritizing patient-centered objectives will result in a thorough understanding of the treatments effects and encompassing quality of life [99].

Conclusion

This study focuses on the complex interactions that exist between neurotransmitter receptors and the effectiveness of antipsychotic medications in treating psychosis associated with AD. The intricate nature of psychosis in AD is highlighted by the neuropathological alterations in neurotransmitter systems, specifically in glutamate, serotonin, and dopamine, which calls for focused therapeutic interventions. The study examined the pharmacodynamic variations across antipsychotic drugs in connection to their receptor affinity, highlighting the necessity of a comprehensive comprehension of their influence on clinical results. Treatment difficulties, such as the possibility of negative cognitive and motor consequences, emphasize the careful balancing act needed when administering antipsychotics to individuals with AD. Although novel tactics targeting receptors show promise in reducing side effects, it is imperative to address current information gaps and conduct customized clinical trials for this population. The analysis concludes that a more tailored approach is required to optimize the treatment of AD-related psychosis and reduce side effects in this vulnerable population. These discoveries should lead to more focused and customized treatment plans as research continues, which will eventually improve the lives of those who have Alzheimer's and the people who care for them.

Abbreviations

AD	Alzheimer's disease
ARP	Alzheimer's-related psychosis
CitAD	Citalopram for Agitation in Alzheimer's Disease Study
PET	Positron emission tomography
EPS	Extrapyramidal symptoms
ISTAART	Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment
PFC	Prefrontal cortex
D3	Dopamine 3
RCT	Randomized controlled trial
M1/M4	Muscarinic acetylcholine receptor
GWAS	Genome-wide association study
SNP	Single nucleotide polymorphism
APOE	Apolipoprotein E
FDA	Food and Drug Administration
5HT	5-Hydroxytryptamine
R	Receptor
NPI	Neuropsychiatric Inventory
CY	Cytochrome
NMDA	N-Methyl-D-aspartate glutamate receptors
TMS	Transcranial magnetic stimulation
GABAergic	Gamma-aminobutyric acid

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Declaration of figures authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

Author contributions

In the present review, BS analyzed the data related to disease, treatment approaches and future directions and was the most important contribution in making the manuscript. SD, AM, DSR, PKT and NK performed the systematic evaluation and elaborated on the conclusion. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate

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Consent for publications

Not applicable.

Competing interests

The authors announce that they have no competing interests.

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