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The Role of Antipsychotic Agents in Dementia – Associated Neuropsychiatric Symptoms: Efficacy, Safety, and Deprescribing Strategies

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Abstract

Background. Dementia syndromes involve cognitive and functional decline and frequent neuropsychiatric symptoms, including agitation, aggression, hallucinations, delusions, anxiety, irritability and sleep disturbance. These symptoms increase caregiver burden, institutionalization, healthcare use and loss of quality of life. Antipsychotics remain relevant but controversial because benefits are modest and risks substantial.

Aim. This review summarizes evidence and guideline recommendations on the role, indications, monitoring and deprescribing of antipsychotics in dementia-related neuropsychiatric symptoms.

Material and methods. This narrative review was based on selected guidelines, systematic reviews, network meta-analyses, randomized trials and observational studies on antipsychotic use in dementia-related neuropsychiatric symptoms.

Results. Antipsychotics should not be routine first-line treatment. Before pharmacotherapy, reversible causes such as pain, delirium, infection, dehydration, drug effects and environmental triggers should be assessed. Psychosocial and environmental interventions remain fundamental. Antipsychotics may be considered only in selected patients with severe agitation, aggression or psychosis causing distress or risk of harm. Evidence supports modest efficacy mainly for agitation and aggression, whereas effects on psychosis are less consistent. Risperidone is a well-established option for severe aggression and agitation in Alzheimer's disease, while brexpiprazole has emerged as an option for agitation in Alzheimer's dementia. Treatment requires individualized risk-benefit assessment because of sedation, extrapyramidal symptoms, falls, cerebrovascular events, pneumonia, acute kidney injury, thromboembolism and mortality.

Conclusions. Antipsychotics have a restricted but important role in dementia care. Their use should be symptom-targeted, time-limited, monitored and linked to deprescribing.

Key words: dementia; neuropsychiatric symptoms; behavioral and psychological symptoms of dementia; antipsychotics; agitation; psychosis; brexpiprazole; risperidone; deprescribing.

1. Introduction

Dementia is an acquired clinical syndrome characterized by progressive impairment of cognition, functional autonomy and adaptive behavior. It results from heterogeneous neurodegenerative, vascular and mixed pathologies, with Alzheimer's disease representing the most frequent cause and contributing to approximately 60–70% of cases worldwide [1]. Dementia has become one of the leading causes of disability and dependency in older adults, and its epidemiological impact is expected to increase substantially over the coming decades [1,2].

The clinical phenotype of dementia extends beyond cognitive impairment. Neuropsychiatric symptoms, also termed behavioral and psychological symptoms of dementia (BPSD), include agitation, aggression, delusions, hallucinations, apathy, depression, anxiety, irritability, disinhibition, aberrant motor behavior, sleep disturbance and appetite changes [3,18]. These symptoms are associated with accelerated functional decline, increased caregiver burden, institutionalization, poorer quality of life and greater use of health and social care resources [3,18,19]. The high prevalence of neuropsychiatric symptoms is supported by longitudinal community data from the Cache County Study, in which the five-year period prevalence of any neuropsychiatric symptom reached 97% among individuals with dementia [3]. Other epidemiological studies similarly show that behavioral and psychological symptoms occur in most patients during the disease course, although point prevalence varies according to dementia subtype, severity, setting and measurement instrument [18,19].

Psychotic symptoms form a clinically important but heterogeneous subgroup of dementia-associated neuropsychiatric symptoms. In Alzheimer's disease, psychosis usually presents as non-bizarre delusions, visual hallucinations, or misidentification phenomena rather than the complex Schneiderian symptomatology typical of schizophrenia spectrum disorders [20]. In a systematic review of psychotic symptoms across dementia etiologies, the overall frequency of psychotic symptoms ranged from 34% to 63%, with dementia with Lewy bodies showing a particularly strong association with hallucinations and Alzheimer's disease showing frequent delusions and misidentification phenomena [5]. A review focused on Alzheimer's disease reported that delusions and hallucinations occur in approximately half of affected individuals during the illness course [20]. These epidemiological observations are clinically relevant because psychosis in dementia is associated with distress, higher care complexity, faster deterioration and greater risk of institutional placement [20,21].

The management of neuropsychiatric symptoms is complicated by their multifactorial pathogenesis. Agitation may reflect pain, delirium, infection, urinary retention, constipation, hypoxia, sleep disruption, sensory impairment, medication toxicity, environmental stressors or unmet psychosocial needs [8–10]. Psychotic symptoms may arise from dementia pathology, delirium, sensory deprivation, dopaminergic treatment, sleep disturbance or comorbid psychiatric illness [9,20]. Therefore, symptomatic suppression without etiological formulation may expose patients to pharmacological harm while leaving the actual precipitant untreated.

Antipsychotic agents occupy a narrow and high-risk position in this therapeutic landscape. They may reduce severe agitation, aggression or psychosis in selected patients, but average benefits are modest and the probability of clinically meaningful response is limited [11,12]. Conversely, adverse outcomes are common and clinically significant, particularly in frail older adults with multimorbidity and polypharmacy [6,7,13]. The central clinical question is therefore not whether antipsychotics can be prescribed in dementia, but when their short-term symptomatic benefit is sufficiently probable and sufficiently important to justify class-related harm.

Research Objective. The objective of this review is to define the contemporary role of antipsychotic agents in the treatment of neuropsychiatric symptoms associated with dementia syndromes, with emphasis on guideline-based indication setting, efficacy, safety, monitoring and deprescribing.

Research Problems. This review addresses the following questions: which dementia-associated neuropsychiatric symptoms are most relevant to antipsychotic prescribing; when do major guidelines consider antipsychotic treatment justified; which antipsychotic agents have the strongest evidence; what risks should determine patient selection and monitoring; and how should clinicians approach deprescribing after stabilization or non-response?

2. Research materials and methods

2.1. Participants

This manuscript is a narrative review and did not involve the recruitment of human participants. The reviewed populations were those included in guidelines, randomized controlled trials, systematic reviews, network meta-analyses and observational studies concerning adults with dementia and clinically relevant neuropsychiatric symptoms. The evidence base primarily concerned Alzheimer's disease, vascular dementia and mixed dementia. Specific considerations for dementia with Lewy bodies and Parkinson's disease dementia were included because these syndromes carry distinctive risks related to antipsychotic sensitivity [8,22,23].

2.2. Procedure, literature search and source selection

The review was developed through targeted source selection focused on open-access or freely accessible literature relevant to antipsychotic treatment in dementia-associated neuropsychiatric symptoms. Priority was given to major guidelines, high-quality systematic reviews, network meta-analyses, randomized controlled trials and large pharmacoepidemiological studies.

The predefined core sources were: NICE NG97; the American Psychiatric Association guideline on antipsychotics for agitation or psychosis in dementia; the European Academy of Neurology guideline on medical management issues in dementia; the Cochrane review on antipsychotics for agitation and psychosis in Alzheimer's disease and vascular dementia; the BMJ Mental Health network meta-analysis of second-generation antipsychotics by Lü et al.; CATIE-AD; the BMJ matched cohort study on multiple adverse outcomes; the deprescribing guideline by Bjerre et al.; the meta-analysis of antipsychotic discontinuation by Roche et al.; and the post hoc analysis of brexpiprazole in Alzheimer's dementia by Tariot et al. [8–17].

Additional sources were included to contextualize epidemiology, psychosis prevalence, dementia subtype-specific risks, non-pharmacological treatment and drug-specific evidence [1–7,18–25].

2.3. Data collection and analysis

Data were extracted narratively. The following domains were prioritized: prevalence of dementia and neuropsychiatric symptoms; prevalence and phenomenology of psychotic symptoms; guideline indications for antipsychotic use; recommended pre-treatment assessment; evidence of efficacy; serious adverse outcomes; agent-specific tolerability; dementia subtype considerations; treatment duration; monitoring; and deprescribing.

Because this is a narrative review, no pooled quantitative analysis was performed. Study findings were interpreted according to hierarchy of evidence, clinical relevance, population applicability and consistency across guidelines.

2.3.1. AI

AI-based assistance (ChatGPT) was used to support manuscript organization, academic English refinement, terminology consistency and citation placement.

3. Research results

3.1. Epidemiology of dementia and dementia-associated neuropsychiatric symptoms

The global burden of dementia is substantial and increasing. WHO estimated that 57 million people lived with dementia in 2021, with more than 60% residing in low- and middle-income countries [1]. Global Burden of Disease modelling estimated 57.4 million dementia cases in 2019 and projected an increase to 152.8 million cases by 2050 [2]. This increase is expected to occur despite relative stability in age-standardized prevalence, because population ageing and population growth will expand the absolute number of affected individuals [2]. The public health relevance of dementia is further amplified by dependency, informal caregiving, disability and high economic costs [1,2].

Neuropsychiatric symptoms are highly prevalent across dementia syndromes. The Cache County Study reported that the point prevalence of any neuropsychiatric symptom increased from 56% at baseline to 76–87% during later visits, while the five-year period prevalence reached 97% [3]. In that cohort, depression, apathy and anxiety had particularly high period prevalence, and apathy showed increasing prevalence as dementia progressed [3]. A community-based systematic review confirmed that behavioral and psychological symptoms are common in dementia, although prevalence estimates vary substantially depending on assessment setting, dementia subtype, severity and instrument [19]. This heterogeneity is expected because neuropsychiatric symptoms are not a single entity but a cluster of partially overlapping syndromes with distinct neurobiological, environmental and psychosocial determinants [18,19].

Psychotic symptoms require separate epidemiological attention because they frequently drive antipsychotic prescribing. In Alzheimer's disease, psychosis often includes delusions of theft, persecution, abandonment, infidelity or misidentification, and hallucinations are more commonly visual than auditory [20]. A systematic review across dementia etiologies found that psychotic symptoms occurred in 34–63% of cases, with clinically relevant differences between Alzheimer's disease, dementia with Lewy bodies, vascular dementia and

frontotemporal dementia [5]. In the Cache County Study, delusions increased from 18% at baseline to 34–38% at later visits, while hallucinations increased from 10% to 19–24% [3]. These data show that psychosis is not rare in dementia, but they also show why antipsychotic prescribing should not be extrapolated from schizophrenia, because the phenomenology, comorbidity pattern, frailty context and adverse drug susceptibility are fundamentally different [20,21].

Agitation and aggression are also frequent treatment targets. Agitation in dementia is best conceptualized as excessive or inappropriate verbal, vocal or motor activity that is not adequately explained by immediate needs or confusion alone [24]. It is associated with caregiver burden, institutionalization, hospitalization and increased mortality [24]. However, agitation is syndromically non-specific and may signal pain, delirium, environmental mismatch, sensory overload, fear or unmet needs [8,9,24]. This diagnostic ambiguity explains why guidelines consistently place structured assessment and non-pharmacological management before antipsychotic therapy [8–10].

3.2. Guideline-based indications for antipsychotic treatment

Major guidelines are consistent in restricting antipsychotic treatment to severe and clinically consequential presentations. NICE NG97 recommends that before any non-pharmacological or pharmacological treatment for distress in dementia, clinicians should conduct a structured assessment to explore possible reasons for distress and to address clinical or environmental causes such as pain, delirium or inappropriate care [8]. NICE recommends psychosocial and environmental interventions as initial and ongoing management [8]. Antipsychotics should be offered only when the person is at risk of harming themselves or others, or when agitation, hallucinations or delusions cause severe distress [8].

The American Psychiatric Association guideline similarly recommends a careful evaluation of symptom type, frequency, severity, pattern and timing, together with assessment of pain and other modifiable contributors [9]. According to the APA, antipsychotic treatment in non-emergency circumstances should be reserved for symptoms that are severe, dangerous, or associated with significant distress [9]. The guideline also emphasizes shared decision-making, explicit discussion of benefits and harms, use of the lowest effective dose, and discontinuation when adequate response is absent [9].

The European Academy of Neurology guideline endorses a comparable framework. It recommends identifying and treating contributors such as infection, dehydration, pain, pulmonary disease, cardiac disease, medication effects and environmental stressors before initiating antipsychotic treatment [10]. When antipsychotics are considered necessary for severe agitation or aggression with risk of harm, the EAN recommends low starting doses, slow titration, minimal effective dosing, follow-up monitoring and a planned stop date [10].

These recommendations imply that antipsychotics are not indicated for caregiver inconvenience, institutional convenience, wandering without danger, insomnia without psychosis or severe agitation, apathy, mild irritability, nonspecific restlessness, or resistance to care that is not associated with severe distress or risk. Their most defensible indications are severe aggression, dangerous agitation, or psychosis causing severe distress or unsafe

behavior after reversible causes have been assessed and non-pharmacological strategies have been implemented [8–10].

3.3. Evidence of efficacy

The 2021 Cochrane review remains one of the most important syntheses of randomized evidence. It included 24 placebo-controlled trials involving 6090 participants with Alzheimer's disease or vascular dementia and clinically significant agitation, aggression or psychosis [11]. Atypical antipsychotics produced a small reduction in agitation, with a standardized mean difference of -0.21, but probably had negligible effect on psychosis [11]. Typical antipsychotics may slightly improve psychosis, but their effect on agitation is uncertain and the certainty of evidence is lower [11]. These findings support a restrained interpretation: antipsychotics can reduce selected symptoms in some patients, but they do not produce broad or robust improvement across the full spectrum of neuropsychiatric manifestations.

CATIE-AD provides clinically relevant pragmatic trial evidence. In this randomized effectiveness trial, 421 outpatients with Alzheimer's disease and psychosis or agitated and aggressive behavior were assigned to olanzapine, quetiapine, risperidone or placebo [13]. Compared with placebo, olanzapine and risperidone improved some psychiatric and behavioral measures, particularly hostility, suspiciousness and psychosis-related dimensions, but functional abilities, care needs and quality of life did not clearly improve [13]. Discontinuation rates were high, and olanzapine was associated with worsening functional skills among patients continuing treatment at 12 weeks [13]. CATIE-AD therefore supports the concept of symptom-targeted efficacy rather than global clinical restoration.

CATIE-AD also raised concerns about cognition and metabolic burden. A cognitive outcomes analysis found that atypical antipsychotic treatment was associated with worsening in several cognitive measures compared with placebo [25]. A metabolic analysis found weight gain, particularly among females, and unfavorable metabolic changes with olanzapine [26]. These findings reinforce the need to avoid open-ended continuation after limited symptomatic benefit.

The 2024 BMJ Mental Health network meta-analysis by Lü et al. included 20 randomized controlled trials with 6374 participants and compared second-generation antipsychotics for behavioral and psychological symptoms of dementia [12]. Brexpiprazole showed the strongest efficacy signal in the network, aripiprazole had the most favorable acceptability ranking, and olanzapine showed the poorest tolerability [12]. Risperidone remained clinically important because of historical evidence and regulatory status in several jurisdictions [8,12]. Network rankings should nevertheless be interpreted cautiously because trial populations, outcome scales, dementia severity, target symptoms and treatment duration differed across studies [12].

Brexpiprazole represents the most important recent development in this field. In 2023, the United States Food and Drug Administration approved brexpiprazole for agitation associated with dementia due to Alzheimer's disease, making it the first FDA-approved treatment for this indication [15]. In a 12-week randomized clinical trial of 345 patients, brexpiprazole 2 mg or 3 mg daily significantly reduced Cohen-Mansfield Agitation Inventory total scores compared with placebo and was generally well tolerated during the short trial period [16]. In

the 2026 post hoc analysis of pooled short-term and long-term trials, 23.4% of participants had co-occurring psychosis at baseline, and brexpiprazole improved agitation both in participants with psychosis and those without psychosis [17]. These findings support brexpiprazole as a clinically relevant option for Alzheimer's-related agitation, but they do not justify expansion of antipsychotic use to mild or nonspecific behavioral symptoms [15–17].

3.4. Safety profile and adverse outcomes

The safety profile of antipsychotics is central to decision-making in dementia. The Cochrane review found that atypical antipsychotics increased somnolence, extrapyramidal symptoms, serious adverse events and probably mortality, although mortality estimates were imprecise [11]. Typical antipsychotics increased somnolence and extrapyramidal symptoms, and their safety profile is generally less favorable in frail older adults [11].

Large observational studies extend this risk framework beyond outcomes typically captured in short randomized trials. The 2024 BMJ population-based matched cohort study evaluated 173,910 adults with dementia in England, including 35,339 new antipsychotic users [7]. Antipsychotic use was associated with increased risks of stroke, venous thromboembolism, myocardial infarction, heart failure, fracture, pneumonia and acute kidney injury [7]. The risks were particularly high soon after treatment initiation, and pneumonia showed one of the most clinically important absolute risk differences [7]. These findings are consistent with the biological plausibility of sedation, dysphagia, aspiration, immobility, autonomic effects and cardiovascular vulnerability in older patients with dementia.

Mortality risk has been repeatedly observed. Maust et al. reported that antipsychotic exposure in dementia was associated with increased mortality and provided number-needed-to-harm estimates that varied by agent and dose [6]. The excess mortality signal is clinically important even when absolute risk increase appears modest, because treatment is often initiated in frail patients with limited physiological reserve and because alternative causes of agitation may be modifiable [6,7,9].

Adverse effects differ by agent, receptor profile, dose and patient vulnerability. Haloperidol is associated with a high risk of extrapyramidal symptoms and should generally be restricted to exceptional short-term circumstances involving acute dangerous agitation when safer approaches are not feasible [11]. Risperidone has evidence for aggression and agitation but carries risks of extrapyramidal symptoms, cerebrovascular events, sedation and orthostatic hypotension [8,11,12]. Olanzapine may improve selected symptoms but is limited by sedation, metabolic effects and poorer tolerability [12,13,26]. Quetiapine has weaker evidence for efficacy in general dementia-associated agitation, but it is sometimes considered when parkinsonism or Lewy body disease makes stronger dopamine D2 blockade hazardous [22,23]. Aripiprazole may have relatively favorable acceptability, but akathisia, insomnia and extrapyramidal symptoms remain relevant [12]. Brexpiprazole has favorable short-term randomized evidence in Alzheimer's-related agitation, but long-term real-world safety data in frail, multimorbid populations remain limited [15–17].

3.5. Agent selection and dementia subtype considerations

Agent selection should be individualized according to symptom phenotype, dementia subtype, baseline frailty, cerebrovascular history, parkinsonism, falls risk, swallowing function, renal

vulnerability, cardiac conduction, metabolic profile, drug interactions and prior treatment response [8–12].

Risperidone is one of the best-established agents for persistent aggression and severe agitation in Alzheimer's disease. NICE notes that risperidone has a marketing authorization for short-term treatment of persistent aggression in moderate to severe Alzheimer's disease when non-pharmacological approaches have failed and there is risk of harm [8]. The EAN guideline states that risperidone may be considered a first-line antipsychotic option when pharmacological treatment of agitation or aggressive behavior is unavoidable [10]. This does not mean that risperidone should be used broadly; rather, it means that when antipsychotic treatment is justified, risperidone has one of the more coherent evidence and licensing profiles [8,10,12].

Brexpiprazole should be considered separately because its evidence base is linked to agitation associated with Alzheimer's dementia. Its approval does not apply to all dementia syndromes and does not establish a general indication for dementia-related psychosis without agitation [15]. In practice, brexpiprazole is most relevant when agitation is clearly defined, persistent, clinically significant and inadequately controlled with non-pharmacological strategies [15–17]. The target symptom should be operationalized before treatment, for example by documenting frequency and severity of physical aggression, verbal aggression, pacing, restlessness, repetitive motor behavior or distress-related behavioral escalation [16,17].

Quetiapine occupies a distinct practical position in patients with parkinsonism or suspected Lewy body pathology. Its lower dopamine D2 receptor occupancy may reduce extrapyramidal liability relative to risperidone or haloperidol, but the evidence for robust efficacy in dementia-related agitation is limited [11,12,22]. Therefore, quetiapine should not be considered a strongly evidence-based general treatment for behavioral symptoms. Its use is more defensible when antipsychotic therapy is unavoidable and motor vulnerability strongly constrains options [22,23].

Dementia with Lewy bodies and Parkinson's disease dementia require particular caution. NICE states that antipsychotics can worsen motor features and may cause severe sensitivity reactions in these disorders [8]. Reviews of dementia with Lewy bodies report that severe neuroleptic sensitivity may occur in a substantial proportion of patients and may manifest as profound sedation, confusion, rigidity, worsening parkinsonism, dysautonomia and potentially fatal deterioration [22,23]. Typical antipsychotics, especially haloperidol, should generally be avoided in this context [22,23]. If psychosis is distressing or dangerous and pharmacotherapy is unavoidable, specialist input is advisable, and the lowest possible dose should be used with close monitoring [8,22,23].

3.6. Monitoring, treatment duration and deprescribing

Safe prescribing requires that antipsychotic treatment begin with a defined endpoint. NICE recommends the lowest effective dose for the shortest possible duration and reassessment at least every six weeks [8]. NICE also recommends stopping antipsychotic treatment when there is no clear ongoing benefit after discussion with the person and family members or carers [8]. The APA guideline recommends that if there is no clinically meaningful response after an adequate trial, usually within four weeks at an adequate dose, treatment should be

tapered and discontinued [9]. The APA further recommends an attempt to taper and withdraw medication within approximately four months when clinically appropriate [9].

Baseline assessment should include indication, target symptom, severity, frequency, immediate risk, prior non-pharmacological interventions, potential precipitants, medical comorbidity and current medication burden [8–10]. Particular attention should be paid to delirium, pain, infection, hydration, constipation, urinary retention, hypoxia, sleep disruption, anticholinergic load, benzodiazepine exposure, opioids, dopaminergic therapy, QT-prolonging drugs, orthostatic hypotension, falls history, dysphagia and prior cerebrovascular events [7–10].

During treatment, monitoring should include target symptom response, sedation, gait instability, falls, orthostatic blood pressure, extrapyramidal symptoms, swallowing, hydration, infection signs, cognition, functional capacity and caregiver-observed behavioral change [7–11]. Electrocardiography and electrolyte assessment should be considered in patients with cardiac disease, syncope, arrhythmia history, QT prolongation risk or concomitant QT-prolonging medication [9]. Metabolic monitoring is relevant for second-generation antipsychotics, especially olanzapine and quetiapine, although the urgency and frequency of monitoring should be individualized to prognosis and treatment duration [26].

Deprescribing should be considered part of appropriate prescribing rather than a separate late-stage intervention. The 2018 evidence-based deprescribing guideline by Bjerre et al. recommends deprescribing antipsychotics used for behavioral and psychological symptoms of dementia when symptoms have stabilized after at least three months of treatment or when there has been no adequate response [14]. Suggested tapering strategies include dose reduction by 25–50% every one to two weeks, with slower tapering for patients treated long term or those with severe baseline symptoms [14].

However, deprescribing should not be mechanistic. The 2025 meta-analysis by Roche et al. found that antipsychotic discontinuation increased relapse risk, with a pooled relative risk of 1.52 [17]. The absolute risk appeared particularly relevant in randomized withdrawal settings, suggesting that patients who recently responded and stabilized may be more vulnerable to relapse than those maintained for longer periods without clear ongoing need [17]. Thus, the appropriate conclusion is not that antipsychotics should be continued indefinitely, but that deprescribing should be planned, monitored and individualized.

A clinically defensible deprescribing plan should specify the target symptom that justified treatment, the current symptom status, the tapering schedule, expected withdrawal timeline, relapse criteria, non-pharmacological supports, caregiver instructions and criteria for re-initiation [14,17]. If symptoms recur during tapering, clinicians should reassess for new triggers before automatically reinstating the previous dose. When re-initiation is necessary because of severe relapse or risk of harm, the lowest previously effective dose should be used and a later tapering attempt should remain part of the treatment plan [9,14,17].

4. Discussion

This review supports a restrictive, symptom-targeted and time-limited model of antipsychotic use in dementia. The evidence base does not support antipsychotics as routine treatment for

behavioral disturbance broadly defined. Instead, it supports carefully selected use in patients with severe agitation, aggression or psychosis when symptoms produce danger or severe distress and when reversible contributors have been addressed [8–12].

The first implication is that neuropsychiatric symptoms require diagnostic formulation. A patient who shouts, paces, refuses care or becomes aggressive may have pain, delirium, infection, urinary retention, constipation, hypoxia, sensory misperception, environmental overstimulation, fear or communication failure [8,9,24]. Antipsychotic treatment may reduce visible motor or verbal expression while failing to treat the underlying cause. In such cases, pharmacological suppression can obscure clinical deterioration and increase the risk of pneumonia, falls, dehydration or immobilization [7,8]. This is why structured assessment is not merely a guideline formality but a safety intervention.

The second implication is that non-pharmacological management remains foundational. Psychosocial and environmental interventions are recommended as initial and ongoing treatment because many neuropsychiatric symptoms are context-sensitive and because pharmacological alternatives have limited efficacy and substantial harm [8,24]. Tailored activities, caregiver training, pain treatment, sleep-wake stabilization, sensory optimization, communication strategies and environmental modification should continue even when antipsychotics are temporarily used [8,24].

The third implication is that the expected efficacy of antipsychotics should be discussed in realistic terms. The Cochrane review indicates small average improvements for agitation with atypical antipsychotics and uncertain or negligible effects on psychosis [11]. CATIE-AD suggests that some symptom domains, such as hostility, suspiciousness and paranoid ideation, may improve with selected agents, but quality of life, care needs and function do not reliably improve [13]. Clinicians should therefore avoid framing antipsychotics as disease-modifying or globally stabilizing treatments. They are symptomatic agents for a narrow set of severe target behaviors.

The fourth implication concerns agent selection. Risperidone remains a reference option for severe aggression and agitation in Alzheimer's disease, but cerebrovascular risk, extrapyramidal symptoms and frailty must guide patient selection [8,10–12]. Brexpiprazole has the strongest recent evidence for agitation associated with Alzheimer's dementia and has a specific FDA indication, but it should not be generalized to all dementia syndromes or to all neuropsychiatric symptoms [15–17]. Quetiapine may be useful in selected parkinsonian phenotypes when antipsychotic treatment is unavoidable, but weaker efficacy evidence should be acknowledged [11,12,22]. Olanzapine and haloperidol should be used with particular caution because tolerability and safety concerns often outweigh their modest benefits in frail dementia populations [11–13,26].

The fifth implication is that deprescribing must be integrated into the original prescription. Treatment without a stop date or reassessment plan is inconsistent with NICE, APA and EAN recommendations [8–10]. The Bjerre guideline provides practical tapering strategies, while the Roche meta-analysis adds necessary nuance by showing that discontinuation can increase relapse risk in a subgroup [14,17]. The clinically balanced approach is planned deprescribing with relapse surveillance rather than automatic indefinite continuation or abrupt withdrawal.

Brexpiprazole may alter clinical practice, but it does not alter the ethical structure of antipsychotic prescribing in dementia. Its evidence base provides a more specific pharmacological option for agitation in Alzheimer's dementia, especially where symptoms are severe, persistent and measurable [15–17]. Nevertheless, brexpiprazole retains class-level concerns and should be prescribed with the same emphasis on informed consent, monitoring and time-limited use [15–17].

Several limitations should be acknowledged. Many randomized trials are short, exclude highly frail or medically unstable patients, and use rating-scale outcomes that may not capture patient-centered endpoints such as dignity, comfort, caregiver safety, avoidance of restraint and ability to remain at home. Observational safety studies are vulnerable to confounding by indication, although contemporary matched cohort designs strengthen causal plausibility [7]. Evidence is strongest for Alzheimer's disease and mixed dementia, while dementia with Lewy bodies, Parkinson's disease dementia, vascular dementia and frontotemporal dementia remain less adequately represented in randomized evidence [5,22,23]. Finally, the evidence base is still insufficient to determine which clinical, biological or environmental markers best predict response and harm.

5. Conclusions

Antipsychotic agents have a limited but sometimes necessary role in the treatment of neuropsychiatric symptoms associated with dementia syndromes. Their use should be restricted to severe agitation, aggression or psychosis associated with immediate risk, substantial danger, or severe distress.

Before initiation, clinicians should evaluate and treat reversible contributors, including pain, delirium, infection, dehydration, constipation, urinary retention, sensory impairment, medication adverse effects and environmental triggers. Psychosocial and environmental interventions should be used as initial and ongoing management.

The evidence indicates modest average efficacy, strongest for agitation and aggression and less consistent for psychosis. Risperidone remains one of the best-established agents for severe aggression and agitation in Alzheimer's disease. Brexpiprazole is an important recent addition for agitation associated with Alzheimer's dementia, but its indication should not be generalized to all dementia-related behavioral symptoms. Quetiapine may be considered in selected parkinsonian phenotypes, but its weaker efficacy evidence should be clearly recognized.

Safety concerns are substantial. Antipsychotics in dementia are associated with sedation, extrapyramidal symptoms, falls, pneumonia, acute kidney injury, venous thromboembolism, stroke, myocardial infarction, heart failure, fracture and increased mortality. Dementia with Lewy bodies and Parkinson's disease dementia require particularly cautious prescribing because of neuroleptic sensitivity.

Best practice requires explicit documentation of target symptoms, shared decision-making, low starting dose, slow titration, lowest effective dose, structured monitoring, early reassessment and a predefined deprescribing plan. Deprescribing should be attempted after

stabilization or non-response, but withdrawal should be individualized and monitored because relapse risk is increased in some patients.

The appropriate clinical model is not antipsychotic avoidance under all circumstances, but precise, accountable and time-limited prescribing for the minority of patients in whom the anticipated benefit outweighs substantial harm.

Disclosure

Supplementary Materials

Not applicable.

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Conflicts of Interest

The author declares no conflict of interest.

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