Dementia Is More Than Memory Loss: Neuropsychiatric Symptoms of Dementia and Their Nonpharmacological and Pharmacological Management

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Neuropsychiatric symptoms of dementia (NPS) are a group of noncognitive symptoms that occur in over 90% of individuals with dementia. NPS seem to result from a complex interaction among various biological, psychosocial, and environmental factors, and they are associated with greater morbidity and mortality, higher caregiver burden and burnout, high risk of nursing home placement, and increased cost of care for patients with dementia. Use of standardized assessment tools like the Neuropsychiatric Inventory can assist with qualifying and quantifying NPS. In this review, the authors evaluate the evidence for efficacy and safety of nonpharmacological and pharmacological interventions for treating NPS, mostly based on published meta-analyses. Commonly prescribed medications include atypical antipsychotics, acetylcholinesterase inhibitors, memantine, antidepressants, and mood stabilizers. There are also limited data on cannabinoids, repetitive transcranial magnetic stimulation, and ECT in individuals with NPS. Available evidence indicates that several nonpharmacological interventions are beneficial in the management of NPS and are recommended as first-line treatments. Pharmacotherapy should be reserved for the treatment of more severe or refractory NPS or where nonpharmacological management is not feasible. Atypical antipsychotics have shown mostly modest benefit in reducing NPS, and their use is limited by their adverse effect profiles. Recent investigations suggest potential strategies for preventing or at least reducing the risk of dementia and NPS. The authors conclude with brief guidelines for clinical practice as well as future research.

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The number of people with dementia worldwide is expected to increase from 57 million in 2019 to 153 million in 2050, largely because of population growth and population aging (1). A few years ago, the World Health Organization (WHO) decided to move the dementia diagnosis from the chapter on mental and behavioral disorders to the one on diseases of the nervous system in its ICD-11 draft. This step generated wide protests from national and international scientific mental health associations. In response, the WHO corrected the misstep, and the dementia diagnosis was moved back to its original category (2). It is noteworthy that Auguste Deter, the first patient described by Alzheimer in 1907 as having a distinct disorder, presented with "unprovoked paranoia that her husband was having an affair with a neighbor." Only afterward, she was noticed to have memory problems (3).

Neuropsychiatric symptoms of dementia (NPS) are a group of noncognitive symptoms that occur in over 90% of people with dementia (4). These symptoms and behaviors are unsafe and disruptive, and they impair the care of a person with dementia (5). NPS tend to occur in clusters or syndromes, such as psychosis (delusions and hallucinations), agitation, aggression, depression, anxiety, apathy, disinhibition, motor disturbances, nighttime behaviors, and appetite and eating problems (6, 7). The prevalence of agitation increases with dementia severity, whereas that of psychosis peaks in middle stages and depression remains stable across all levels of severity (8). The most common symptoms of NPS are apathy in Alzheimer's disease (AD), depression in vascular dementia, anxiety in dementia with Lewy bodies, and agitation and aggression in frontotemporal dementia (9). Individuals with AD present with insidious onset and slowly progressive deterioration in memory, speech, personality, and executive functions (10). Vascular dementia is characterized by a stepwise deterioration in cognition, with predominant deficits in attention, information processing, and executive function (11); among these patients, memory, language, and praxis are more variably affected. Lewy body dementia presents with insidious onset and slow decline in cognition, which is associated with fluctuations in cognition and vivid visual hallucinations, spontaneous Parkinsonian symptoms, and rapid eye movement, as well as behavior problems (12). Frontotemporal dementia may manifest with either behavioral and executive deficits or progressive deficits in speech, grammar, word output, semantic knowledge, and naming, depending on the specific variant of the illness (13).

Overall, NPS is associated with a faster progression of the illness and greater morbidity and mortality rates (14). It often results in the placement of adults with dementia in nursing homes and acute care hospitals. NPS increases caregiver distress and depression and can result in reduced caregiver employment. NPS is responsible for one-third of the cost of care for dementia patients, as a result of greater utilization of health services (15). Undiagnosed medical problems such as hypothyroidism, urinary tract infection, pneumonia, and constipation frequently result in or aggravate NPS (14). NPS can be exacerbated by caregivers' mismatched expectations because of a lack of understanding of the illness, leading to negative communication styles, including harsh tone, anger, and yelling (14). Also, environmental factors, such as changes in routine, alterations in environment, and an under- or overstimulating environment, can result in onset or exacerbation of NPS (14).

One of the best studied NPS is psychosis of dementia. It is associated with rapid functional decline, greater caregiver distress, and earlier institutionalization. The prevalence of psychosis is approximately 30% in AD, 75% in Lewy body dementia, 50% in Parkinson's disease, 15% in vascular dementia, and 10% in frontotemporal dementia (16). The widely used diagnostic criteria for psychosis of dementia proposed by Jeste and Finkel (17) were recently revised and broadened to apply to various major and mild neurocognitive disorders (18).

The neurobiology of NPS indicates a complex interaction among different brain circuits (6, 14, 19–21). Psychosis in AD is reportedly associated with increased dopamine D_3 receptor density in the nucleus accumbens, greater striatal dopamine (D_2/D_3), reduced density of serotonin receptors in the prosubiculum and ventral temporal cortex, reduced perfusion in the right angular gyrus and right occipital lobe, and atrophy in the neocortical, lateral frontal, lateral parietal, and anterior cingulate gyri (19, 20). It has been suggested that psychosis of AD may represent a distinct subtype of AD, although the evidence is mixed (22). Patients with prominent apathy have reduced cholinergic receptor binding, lower binding of dopamine transporter, and reduced metabolic activity in parts of the prefrontal cortex (19). Depression in patients with AD is associated with reduced 5-HT_{1A} receptors and GABA levels, greater numbers of $GABA_A$ receptors, reduced noradrenergic neurons in the locus coeruleus and serotoninergic neurons in the raphe nucleus, and reduced cortical thickness and cerebral glucose metabolism in parts of the frontal and parietal cortices (19, 20). Agitation and/or aggression in AD are often associated with 5-HT_{2A} receptor gene polymorphism, greater atrophy of the frontal cortex, insula, amygdala, cingulate gyrus, and hippocampus, and reduced metabolic activity in the cingulate and right lateral frontotemporal cortex. Caution is needed in interpreting the findings mentioned above in view of the limitations of these studies, such as small sample sizes and small effect sizes, various confounding factors that were not controlled for, and the possibility of type I errors. Nonetheless, this type of research can potentially lead to innovative intervention strategies.

Comprehensive assessment of psychiatric, medical, family, personal, and social histories, collateral information from caregivers, and a physical and mental status examination with appropriate laboratory workup can assist in determining the onset and course of illness, possible causes, and risk and prognostic factors for NPS (23, 24). A systematic review of instruments for qualifying and quantifying NPS (25) found no one measure to be superior to others, although the Neuropsychiatric Interview–Clinician was mentioned as one of the most efficient measures.

Below we discuss the evidence for the efficacy and safety of various nonpharmacological and pharmacological interventions for NPS (14).

NONPHARMACOLOGICAL INTERVENTIONS

We found four excellent meta-analyses of nonpharmacological interventions for NPS. A meta-analysis of 23 studies (26) evaluated the effectiveness of community-based nonpharmacological interventions delivered through family caregivers, such as education and skills training of caregivers, activity planning and environmental design, enhancing support for caregivers, self-care technique for caregivers, and collaborative care. The duration of these interventions varied from 6 weeks to 24 months, with a follow-up duration of 3 to 24 months. These interventions reduced the frequency and severity of NPS (effect size=0.34) and slightly reduced the caregiver burden (effect size=0.15).

A network meta-analysis that included 161 studies found that for agitation and aggression in individuals with dementia, multidisciplinary care (standardized mean difference [SMD]=−0.5), massage and touch therapy (SMD=−0.75), and music combined with massage and touch therapy (SMD=−0.91) were clinically more efficacious than usual care. The standardized mean difference is used as a summary statistic in meta-analyses when the included studies assess the same outcome but measure it in different ways. The surface under the cumulative ranking curve (SUCRA) indicated that the highest ranked treatments (SUCRA ≥90%) were outdoor activities for agitation and physical aggression, outdoor activities and massage and touch therapy for verbal aggression, and exercise combined with activities of daily living modification for physical agitation.

A Bayesian network meta-analysis (27) reviewed 63 randomized controlled trials for 11 nonpharmacological interventions for agitation in dementia patients. The intervention periods ranged from 10 days to 15 months, intervention frequency from one to 21 times a week, and duration of each session from 5 to 120 minutes. In the pairwise meta-analysis, when compared to control groups, benefits were noted for massage therapy (SMD=−0.77), animal-assisted intervention (SMD=−0.47), personally tailored intervention (SMD=−0.39), and pet robot intervention (SMD=−0.38). In the network meta-analysis, significant effects were found for massage therapy (SMD=−5.22), light therapy (SMD=−5.25), music therapy (SMD=−3.61), reminiscence therapy

(SMD=−4.59), animal-assisted intervention (SMD=−3.14), and personally tailored intervention (SMD=−2.98). On comparing the rank probability of the efficacy for the different interventions, massage therapy was ranked as first (43%), followed by personally tailored intervention (18%), animal-assisted intervention (16%), and pet robot intervention (11%).

Meng and colleagues' meta-analysis of 31 randomized controlled trials (28) reported a small effect for nonpharmacological interventions on NPS (duration of intervention, 1 to 48 weeks; number of sessions, 4 to 75) (SMD=−0.12). These interventions also reduced NPS during the follow-up period (10 weeks to 96 weeks) (SMD=−0.24) and showed benefit on caregiver reactions to NPS (SMD=−0.27). Tailored interventions involving activities that catered to patients' abilities and interests or offered education and support that met caregivers' needs were more effective in reducing NPS than standardized interventions (SMD=−0.24).

The DICE (describe, investigate, create, and evaluate) intervention, which evaluates NPS using a structured method and includes assessment of underlying causes, planning of care, and follow-up monitoring and is followed by the training and empowerment of caregivers, along with music therapy, were found to be the most promising nonpharmacological treatment approaches for NPS by international Delphi consensus (29).

Summary

Several nonpharmacological interventions have been reported to have small to large effects on NPS and to have very low risk of serious adverse events. Thus, they should be considered first-line treatment in most patients with NPS.

PHARMACOLOGICAL AND BIOLOGICAL THERAPIES

We conducted a literature search of the PubMed database (on April 18, 2022), using the following keywords: dementia, meta-analysis, antipsychotics, acetylcholinesterase inhibitors, memantine, antidepressants, mood stabilizers, cannabinoids, repetitive transcranial magnetic stimulation (rTMS), and electroconvulsive therapy (ECT). Of the 376 articles identified, 28 meta-analyses were found appropriate for inclusion in this review. There were 20 meta-analyses of atypical antipsychotics (Table 1), two each of mood stabilizers and cannabinoids, and one each of acetylcholinesterase inhibitors, memantine, antidepressants, and rTMS for individuals with NPS. We also included some pivotal randomized controlled trials of atypical antipsychotics, including pimavanserin and brexpiprazole, and of ECT.

Atypical Antipsychotics

A meta-analysis (30) reported that the pooled prevalence of antipsychotic use in dementia patients was 27.5%. Despite the plethora of randomized controlled trials for the management of NPS, none of the atypical antipsychotics is currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of NPS in the United States. Risperidone is licensed for the treatment of severe NPS in Australia, Canada, New Zealand, and the United Kingdom (31).

One meta-analysis of 16 placebo-controlled trials of atypical antipsychotics for aggression, agitation, and psychosis in patients with AD (32) reported that risperidone had modest benefit for aggression and psychosis, olanzapine for aggression, anxiety, and euphoria, and aripiprazole for psychosis.

The pivotal Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer's Disease (CATIE-AD) study, the largest (N=421) non-industry-sponsored randomized controlled trial of atypical antipsychotics for psychosis or agitation/aggression in dementia, compared olanzapine, quetiapine, and risperidone with placebo and assessed clinically meaningful outcomes (33). The antipsychotics were no better than placebo for the primary outcome (time to discontinuation for any reason) or the secondary outcome (Clinical Global Impression of Change scale). Time to discontinuation due to lack of efficacy indicated that olanzapine and risperidone were more efficacious than quetiapine and placebo, and time to discontinuation due to adverse events suggested greater safety with placebo.

Schneider and colleagues' meta-analysis (34) evaluated data from five trials each of olanzapine and risperidone and three trials each of aripiprazole and quetiapine in patients with NPS. Risperidone showed benefits on the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), the Cohen-Mansfield Agitation Inventory (CMAI) (35), and the BEHAVE-AD psychosis subscale, but not on the Neuropsychiatric Inventory (NPI) psychosis subscale or the Clinical Global Impressions severity scale (CGI-S). Aripiprazole produced significant improvement on the Brief Psychiatric Rating Scale (BPRS), NPI change scores, and the CMAI. However, no significant effects were noted on the BPRS and NPI psychosis subscales in the aripiprazole and olanzapine trials. One trial with quetiapine showed benefit on the Clinical Global Impression of Change scale but not on the NPI psychosis subscale.

A network meta-analysis (36) included data from 17 studies of aripiprazole, olanzapine, quetiapine, and risperidone. Only aripiprazole was associated with improvements on the NPI compared to placebo, and only aripiprazole and quetiapine showed improvements on the BPRS compared to placebo. Similarly, only aripiprazole and risperidone showed improvements on the CMAI compared to placebo. The SUCRA confirmed these results.

Pimavanserin, a newer antipsychotic that is a selective 5-HT_{2A} receptor inverse agonist/antagonist with lower affinity for the 5-HT_{2C} receptors and negligible affinity for dopaminergic, muscarinic, histaminergic, or adrenergic receptors (37), is approved in the United States for treatment of hallucinations and delusions associated with Parkinson's disease psychosis (38). A 12-week randomized controlled trial (39, 40) compared pimavanserin (34 mg/day) with placebo for the treatment of psychosis in 181 nursing home residents with AD. Pimavanserin was more effective than placebo at

TABLE 1. Studies of efficacy of atypical antipsychotics in patients with neuropsychiatric symptoms of dementia (NPS)[a]

Authors, Year	Study Type	Study Features	Outcomes
Ballard and Waite, 2006 (32)	Meta-analysis	16 RCTs, AD; atypical antipsychotics vs. placebo; one atypical antipsychotic vs. other atypical antipsychotics	Risperidone (N=5) compared to placebo was found to be beneficial in treating total behaviors (BEHAVE-AD and NPI total score [0.5 mg/day, p=0.01; 1.0 mg/day, p=0.004; 2.0 mg/day, p=0.01]), beneficial in treating aggression (CMAI [1 mg/day, p=0.007; 2 mg/day vs. 1 mg/day, p=0.01], BEHAVE-AD aggressiveness subscore [1 mg/day, p=0.0002; 2 mg/day, p<0.0001]), and beneficial in treating psychosis (BEHAVE-AD subscore [three trials] and NPI subscore [one trial] [1 mg/day, p=0.01]) Olanzapine (N=5) (5–10 mg/day) compared to placebo appeared to improve aggressive behaviors (NPI-NH aggression domain, p=0.03), anxiety (NPI-NH anxiety domain, p=0.01), and euphoria (NPI-NH euphoria/elation domain, p=0.05) Aripiprazole (N=3, but data were available from only one study) (2–15 mg/day) compared to placebo appeared to improve psychosis (BPRS psychosis domain, p=0.03)
Schneider et al., 2006 (33)	RCT	AD; olanzapine, quetiapine, and risperidone vs. placebo	Discontinuation of treatment for any reason: no significant differences between the three antipsychotics—olanzapine (median=8.1 weeks), quetiapine (median=5.3 weeks), and risperidone (median=7.4 weeks)—compared to placebo (median=8.0 weeks) (p=0.52) Median time to discontinuation of treatment due to lack of efficacy: superiority for olanzapine (median=22.1 weeks) and risperidone (median=26.7 weeks) compared to quetiapine (median=9.1 weeks) and placebo (median=9.0 weeks) (p=0.002) CGIC scale: no significant difference between olanzapine (32%), quetiapine (26%), risperidone (29%), and placebo (21%) (p=0.22)
Schneider et al., 2006 (34)	Meta-analysis	15 RCTs, dementia; atypical antipsychotics vs. placebo	Aripiprazole showed benefits on BPRS change scores (p=0.002), NPI change scores (p=0.02), and the CMAI (p=0.002), but no benefits on the BPRS psychosis subscale (p=0.14) or NPI psychosis subscale (p=0.08) Olanzapine showed no benefits on BPRS change score (p=0.24), NPI change score (p=0.25), BPRS psychosis subscale (p=0.38), or NPI psychosis subscale (p=0.97) Quetiapine showed benefits on the CGIC (p=0.005), but no benefits on the BPRS (p=0.08), the PANSS-EC (p=0.12), or the NPI psychosis subscale (p=0.97) Risperidone showed benefits on the BEHAVE-AD (p=0.0008), BEHAVE-AD psychosis subscale (p=0.0002), and CMAI (p<0.00001), but no benefit on the NPI psychosis subscale (p=0.47)
Yury and Fisher, 2007 (79)	Meta-analysis	7 RCTs, dementia; atypical antipsychotics vs. placebo	The mean effect size for primary outcome measures was 0.45 for atypical antipsychotics and 0.32 for placebo; the mean effect size for all the measures of behavioral problems was 0.43 for atypical antipsychotics and 0.26 for placebo
Katz et al., 2007 (80)	Meta-analysis	4 RCTs, AD; risperidone vs. placebo	On the BEHAVE-AD psychosis subscale, effect sizes were 0.87 for risperidone and 0.57 for placebo; at the endpoint, the estimated effect size between the two groups was 0.15; on the CGI scale, at the endpoint, the estimated effect size between risperidone and placebo was 0.17; among individuals with more severe symptoms, the effect sizes were 1.14 for risperidone and 0.61 for placebo; at the endpoint, the estimated effect size between the two groups was 0.29
Sultzer et al., 2008 (78)	RCT	Olanzapine, quetiapine, and risperidone vs. placebo	On NPI total score, olanzapine and risperidone were better than placebo (olanzapine, p=0.007; risperidone, p<0.001); on the CGIC, risperidone was better than placebo (p<0.001); on the BPRS hostile suspiciousness factor, olanzapine and risperidone were better than placebo (olanzapine, p=0.006; risperidone, p=0.003); on the BPRS psychosis factor, risperidone was better than placebo (p=0.010); on the BPRS withdrawn depression factor, olanzapine was worse than placebo (p=0.003); there were no differences between the antipsychotics and placebo on the BPRS cognitive dysfunction factor (p=0.14) and the Cornell Depression Scale (p=0.64)

continued

TABLE 1, *continued*

Authors, Year	Study Type	Study Features	Outcomes
Cheung and Stapelberg 2011 (81)	Meta-analysis	5 RCTs, dementia; quetiapine vs. placebo	NPI total score: mean difference=−3.05 between quetiapine and placebo; CGIC score: mean difference=−0.31 between quetiapine and placebo
Maher et al., 2011 (82)	Meta-analysis	18 RCTs, dementia; atypical antipsychotics vs. placebo	For NPS, effect sizes for aripiprazole, olanzapine, and risperidone were 0.12–0.20, and for quetiapine, 0.11; for psychosis, effect sizes were 0.20 for aripiprazole, 0.05 for olanzapine, 0.05 for risperidone, and −0.03 for quetiapine
Ma et al., 2014 (83)	Meta-analysis	16 RCTs, dementia; atypical antipsychotics vs. placebo	For atypical antipsychotics compared to placebo, the weighted mean difference was −1.58 on the BPRS, −1.84 on the CMAI, −2.8 on the NPI, −0.32 on the −0.32, and −0.19 on the CGI-S
Wang et al., 2015 (84)	Meta-analysis	6 RCTs, AD; atypical antipsychotics vs. placebo	For atypical antipsychotics compared to placebo, on NPI total score, SMD=0.21; for aripiprazole, SMD=−0.20; for olanzapine, SMD=−0.18
Smeets et al., 2018 (85)	Meta-analysis	16 RCTs, dementia; atypical antipsychotics vs. placebo	For agitation when measured with agitation outcome scales, atypical antipsychotics showed negligible effects (SMD=−0.15); for psychosis when measured with psychosis outcome scales, atypical antipsychotics showed negligible effects (SMD=−0.11); on any NPS, a small effect was observed on agitation (SMD=−0.29), and a negligible effect on psychosis (SMD=−0.13); on generic NPS scales, a small effect was observed on agitation (SMD=−0.22), and a negligible effect on psychosis (SMD=−0.11)
Yunusa et al., 2019 (36)	NMA	17 RCTs, dementia; atypical antipsychotics vs. placebo	Aripiprazole: improvements on the NPI (SMD=−0.17), the BPRS (SMD=−0.20), and the on CMAI (SMD=−0.30); olanzapine: no improvements on the NPI, BPRS, or CMAI; quetiapine: no improvements on the NPI, improvements on the BPRS (SMD=−0.24), and no improvements on the CMAI; risperidone: no improvements on the NPI or the BPRS, and improvements on the CMAI (SMD=−0.26); there were no statistically significant differences between the antipsychotics on the NPI, BPRS, or CMAI In the surface under the cumulative ranking curve (SUCRA), the highest probability of effectiveness on the NPI was for aripiprazole (85.3%); on the BPRS, for quetiapine (80.2%) and aripiprazole (72.9%); and on the CMAI, for aripiprazole (73.8%) and risperidone (68.6%)
Ballard et al., 2018 (39) and 2019 (40)	RCT	Pimavanserin vs. placebo	At week 6, the NPI-NH psychosis score was −3.76 for pimavanserin and −1.93 for placebo (p=0.045) Among patients with more severe symptoms at baseline (NPI-NH psychosis score ≥12), the mean change from baseline was −10.15 for pimavanserin and −5.72 for placebo (p=0.011); pimavanserin was better than placebo in treating hallucinations (p=0.046) and delusions (p=0.034) Among patients with mild psychotic symptoms (NPI-NH psychosis score <12), the mean change from baseline was −0.58 for pimavanserin and −0.16 for placebo (p=0.694); NPI-NH total scores did not differ between the pimavanserin and placebo groups either at 6 weeks or 12 weeks At the end of the study period (week 12), no benefit was noted for the pimavanserin group compared to placebo group among the overall study population (p=0.561) or among those with more severe symptoms (NPI-NH psychosis score ≥12) (p=0.497)
Grossberg et al., 2020 (41)	2 RCTs	Brexpiprazole vs. placebo	In study 1, compared to placebo, on CMAI total score, there was a benefit for brexpiprazole at 2 mg/day (p=0.04), but not at 1 mg/day (p=0.90); on the CGI-S, no benefits were noted for brexpiprazole at either 2 mg/day (p=0.16) or 1 mg/day (p=0.44) In study 2, compared to placebo, on CMAI total score, no benefit was noted for brexpiprazole at 0.5–2 mg/day (p=0.15); on the CGI-S, post analyses showed benefit with brexpiprazole (p<0.001) among individuals who were titrated to 2 mg/day over 4 weeks

[a] BEHAVE-AD=Behavioral Pathology in Alzheimer's Disease Rating Scale; BPRS=Brief Psychiatric Rating Scale; CGI=Clinical Global Impressions Scale; CGIC=Clinical Global Impression of Change scale; CGI-S=Clinical Global Impressions severity scale; CMAI=Cohen-Mansfield Agitation Inventory; NMA=network meta-analysis; NPI=Neuropsychiatric Inventory; NPI-NH=Neuropsychiatric Inventory–Nursing Home Version; PANSS-EC=Positive and Negative Syndrome Scale, excited component; RCT=randomized controlled trial; SMD=standardized mean difference.

week 6, but not at week 12, on the Neuropsychiatric Inventory–Nursing Home Version (NPI-NH) psychosis score and among individuals with higher baseline levels of hallucination and delusions, but not for mild psychotic symptoms. At weeks 6 and 12, total score on the NPI-NH did not differ between the two groups.

There have been two multicenter parallel-arm randomized controlled trials of brexpiprazole, another newer atypical antipsychotic, which is a partial agonist at serotonin 5-HT_{1A} and dopamine D_2 receptors and an antagonist at serotonin 5-HT_{2A} and noradrenaline α_{1B}/α_{2C} receptors, in AD patients with agitation (41). Study 1 showed greater improvement with brexpiprazole at 2 mg/day, but not at 1 mg/day, compared to placebo on CMAI total score, but no benefit with either dosage on the CGI-S. In study 2, there was no benefit with brexpiprazole at 0.5–2 mg/day on CMAI total score, but there were improvements in CGI-S score among individuals whose dosage was titrated to 2 mg/day over 4 weeks (41).

Adverse Effects of Atypical Antipsychotics in Patients With NPS

Table 2 summarizes studies of adverse effects of atypical antipsychotics in patients with NPS.

Death. In 2005, the FDA issued a public health advisory on an association between treatment of NPS with atypical antipsychotics—aripiprazole, olanzapine, quetiapine, risperidone, clozapine, and ziprasidone—and increased mortality (42). The advisory stated that among individuals with NPS, 15 studies showed numerical increases in mortality in the drug-treated compared to the placebo-treated groups. Most of these deaths were from heart-related events (e.g., heart failure and sudden death) or infections (mostly pneumonia). The FDA asked the manufacturers of these drugs to add a boxed warning to their labeling describing the risks and indicating that these drugs are not approved for the treatment of NPS. This warning was subsequently extended to all antipsychotics (43).

A meta-analysis of nine epidemiological studies in patients with AD (44) reported a greater risk of death among individuals treated with antipsychotics (conventional or atypical) compared to those who were not. In a retrospective cohort study (45) of 22,890 older individuals who had received antipsychotic medication between 1994 and 2003, mortality was higher with conventional than with atypical antipsychotics. The relative risks (hazard ratios) were higher with higher versus lower dosages of the conventional antipsychotics among patients without versus with dementia and among individuals not in nursing homes versus those in nursing homes. A registry-based cohort study from Sweden (46) also found that among individuals with vascular dementia and LBD, the mortality rate was higher with conventional compared to atypical antipsychotics, while the converse was true for individuals with AD. The previously mentioned network meta-analysis (36) reported that the risk of death was similar with the various atypical antipsychotics and placebo, but the SUCRA indicated lowest probability of mortality with risperidone, followed by aripiprazole, quetiapine, and olanzapine, when compared to placebo.

Cerebrovascular adverse events (CVAEs). In post hoc analyses of randomized trials, Herrmann and Lanctôt (47) found that the exposure-adjusted CVAE incidence rate among elderly patients with dementia treated with risperidone, olanzapine, or placebo was significantly greater in the olanzapine group compared to the placebo group. The rate of serious CVAEs (causing death, being life-threatening, requiring hospitalization, and/or leading to persistent disability) with risperidone was nonsignificantly higher compared to placebo, and the rates of nonserious CVAEs were significantly higher with risperidone than with placebo.

In a population-based retrospective cohort study (48), the rates of ischemic strokes did not differ significantly between dementia patients treated with conventional versus atypical antipsychotics, including those who received two or more consecutive prescriptions. A meta-analysis of five population-based studies (49) also found no significant difference in the relative risk for CVAEs or stroke among persons with dementia receiving conventional versus atypical antipsychotics. A meta-analysis of 10 observational studies (50) found that exposure to any antipsychotic medication was associated with a significantly increased risk for CVAEs, even when the analysis was restricted to older individuals with dementia. Finally, Yunusa and colleagues' network meta-analysis (36) indicated that, compared to placebo, olanzapine and risperidone (but not aripiprazole and quetiapine) were associated with a significantly increased risk of CVAEs. With SUCRA, the lowest probability of CVAEs was for aripiprazole followed by quetiapine, risperidone, and olanzapine compared to placebo.

Cognition. The data from the CATIE-AD study showed a decline in cognition among patients with AD treated with olanzapine, quetiapine, or risperidone compared to placebo, on multiple cognitive measures, including the Mini-Mental State Examination (MMSE), the BPRS cognitive subscale, and a cognitive summary score summarizing change on 18 cognitive tests (51). A meta-analysis of 10 randomized controlled trials of antipsychotics for the treatment of NPS (52) reported that the use of atypical antipsychotics tended to cause cognitive worsening compared to placebo. The longer the duration of the trial, the greater was the cognitive impairment. Higher baseline score on the MMSE was associated with greater cognitive worsening with antipsychotics compared to placebo.

Effects of Withdrawal of Antipsychotics

Table 3 summarizes studies of withdrawal of antipsychotics in patients with NPS.

A meta-analysis of 10 trials (53, 54) found that among individuals with dementia, withdrawal of antipsychotics may

TABLE 2. Studies of adverse effects of atypical antipsychotics in patients with neuropsychiatric symptoms of dementia (NPS)[a]

Category, Authors, Year	Study Type	Study Features	Outcomes
Death			
Schneider et al., 2005 (91)	Meta-analysis	15 RCTs, dementia; atypical antipsychotics vs. placebo	Odds of death were greater among individuals randomized to receive medications (118, 3.5%) compared to those receiving placebo (40, 2.3%); OR=1.54 (p=0.02); risk difference=0.01 (p=0.01) The risk differences for death among individuals receiving medications compared to placebo were as follows: aripiprazole vs. placebo, 0.01 (p=0.20); olanzapine vs. placebo, 0.01 (p=0.07); quetiapine vs. placebo, 0.02 (p=0.22); risperidone vs. placebo 0.01 (p=0.33); the overall RR was 1.65 (p=0.003) No heterogeneity was observed between trials of individuals with higher cognitive function (MMSE score >10) when compared to individuals with lower cognitive function; between individuals with psychosis of AD when compared with those trials that did not select patients with psychosis; or between trials of inpatients compared to outpatients
Mittal et al., 2011 (42); Rubino et al., 2020 (43)	Review from FDA advisory	17 RCTs, dementia; antipsychotics vs. placebo	15 studies showed an increases in mortality in drug-treated groups compared to placebo-treated groups (1.6–1.7 times); most deaths were due to heart-related events (e.g., heart failure sudden death) or infections (e.g., pneumonia) Manufacturers were required to have a boxed warning describing the risks and indicating that these drugs are not approved for treatment of NPS; the warning was subsequently extended to all antipsychotics
Zhai et al., 2016 (44)	Meta-analysis	9 epidemiological studies, AD; antipsychotic medications vs. no antipsychotics	In pooled data from eight observational studies, the risk for death was greater among individuals treated with antipsychotics compared to those who were not (RR=1.36); mortality rates among individuals treated with atypical or conventional antipsychotics were the same (RR=1.75)
Wang et al., 2005 (45)	Retrospective cohort study	Conventional vs. atypical antipsychotics	Mortality among patients treated with conventional antipsychotics was higher than with atypical antipsychotics at all intervals studied; ≤180 days: RR=1.37; <40 days: RR=1.56; 40–79 days: RR=1.37; 80–180 days: RR=1.27 HRs were higher 1) when higher dosages of the conventional antipsychotic (greater than the median) were used compared to lower dosages (1.73 vs. 1.14); 2) less than 40 days compared with 80–180 days after beginning therapy (1.56 vs. 1.27); 3) among individuals without dementia compared to those with dementia (1.45 vs. 1.29); and 4) among individuals not in a nursing home compared to those in a nursing home (1.42 vs. 1.26)
Schwertner et al., 2019 (46)	Registry-based cohort study	Dementia; conventional and atypical antipsychotic use vs. nonuse of antipsychotics	The use of conventional and atypical antipsychotics was associated with increased mortality risk compared to no antipsychotic use (HR=1.4); antipsychotic use was associated with increased risk of mortality compared with nonuse of antipsychotics in AD (atypical: HR=1.5), in mixed dementia (conventional: HR=1.3; atypical: HR=1.3), in unspecified dementia (atypical: HR=1.3), in vascular dementia (conventional HR=1.6 vs. atypical HR=1.3) In AD, for mortality risk with conventional vs atypical antipsychotic use, the HR was 0.7; in LBD, for mortality risk with conventional antipsychotic use vs. nonuse of antipsychotics the HR was 1.4, and for risk with atypical antipsychotic use vs. nonuse of antipsychotics, the HR was 1.4
Yunusa et al., 2019 (36)	NMA	17 RCTs, dementia; atypical antipsychotics vs. placebo	For risk of death, no difference between any of the antipsychotics or between the antipsychotics and placebo; SUCRA indicated that the highest probability of safety in terms of mortality was 87.3% for placebo, 55.4% for risperidone, 37.9% for aripiprazole, 37.1% for quetiapine, and 32.4% for olanzapine
Cerebrovascular adverse events			
Herrmann and Lanctôt 2005 (47)	Post hoc analyses of pooled results from RCTs	11 RCTs, dementias; olanzapine and risperidone vs. placebo	Olanzapine had a higher exposure-adjusted CVAE incidence in the drug group (15/1178, 1.3%) compared to the placebo group (2/478, 0.4%) (p=0.016); risperidone had higher rates of serious CVAEs in the drug group (15/1009, 1.5%) compared to the placebo group (4/712, 0.6%) (p=0.27); rates of nonserious CVAEs were higher in the drug group (18/1009, 1.8%) compared to the placebo group (4/712, 0.6%) (p=0.026)

continued

TABLE 2, *continued*

Category, Authors, Year	Study Type	Study Features	Outcomes
Rao et al., 2016 (49)	Meta-analysis	Five population-based studies, dementia; atypical and conventional antipsychotics vs. nonuse of antipsychotics	CVA: no difference in risk among individuals treated with atypical antipsychotics compared to conventional antipsychotics (RR=1.02); no difference in risk among individuals who were treated with atypical antipsychotics compared to no antipsychotics (RR=0.95) Stroke: no difference in risk among individuals treated with atypical antipsychotics compared to conventional antipsychotics (p=0.96)
Hsu et al., 2017 (50)	Meta-analysis	10 observational studies, dementia; atypical antipsychotics and conventional antipsychotics	Use of any antipsychotic was associated with an increased risk of CVA (OR=1.45); the risk was increased among the elderly (OR=1.49) and among individuals with dementia (OR=1.17)
Yunusa et al., 2019 (36)	NMA	17 RCTs, dementia; atypical antipsychotics vs. placebo	Compared to placebo, risk of CVAEs was increased for olanzapine (OR=4.28) and risperidone (OR=3.85); compared to placebo, there was no increased risk of CVAEs for aripiprazole (OR=1.09) or quetiapine (OR=1.36); none of the included antipsychotics were significantly different from each other on the risk of CVAEs According to the SUCRA, the highest probability of safety on CVAEs with antipsychotics compared to placebo was for aripiprazole (69.1%), followed by quetiapine (65.1%), risperidone (19.6%), and olanzapine (15.8%)
Gill et al., 2005 (48)	Population-based retrospective cohort study	Dementia; atypical vs. conventional antipsychotics	Rates of ischemic stroke were no different among individuals treated with atypical antipsychotics compared to individuals treated with conventional antipsychotics (aHR=1.01) The risk of stroke among individuals receiving conventional antipsychotics compared to those treated with olanzapine (aHR) was 0.91; compared to those treated with quetiapine, 0.78; and compared to those treated with risperidone, 1.04. The risk of stroke among chronic atypical antipsychotic users compared to chronic conventional antipsychotic users (aHR) was 0.89
Cognition			
Wolf et al., 2017 (52)	Meta-analysis	10 RCTs, dementia; antipsychotics vs. placebo	The use of atypical antipsychotics showed a tendency for cognitive worsening compared to placebo (SMD=−0.109); only 2 of the 10 studies showed significant effects on cognition (one study for aripiprazole [SMD=−0.498] and one study for olanzapine [SMD=−0.411]) The test for heterogeneity was significant among the aripiprazole (p=0.03) and olanzapine studies (p=0.01) but not in the quetiapine (p=0.69) and risperidone (p=0.89) studies; when the two studies (one for aripiprazole and one for olanzapine) were excluded, the SMD was 0 (p=0.95) There was correlation between cognitive impairment and treatment duration (p<0.02): the longer the duration of study, the greater the cognitive impairment; the higher baseline cognition as measured by MMSE, the greater the cognitive worsening with antipsychotic treatment (p<0.005); these correlations disappeared when the two studies with significant effects on cognition were removed
Vigen et al., 2011 (51)	RCT	AD; olanzapine, quetiapine, and risperidone vs. placebo	There was a decline in cognition among individuals with AD who were treated with olanzapine, quetiapine, or risperidone compared to individuals treated with placebo, on the MMSE (p=0.004), the BPRS cognitive subscale (p=0.05), and a cognitive summary score summarizing change on 18 cognitive tests (p=0.004)
Pimavanserin			
Ballard et al., 2018 (39)	RCT	Pimavanserin vs. placebo	Any adverse event: 98% for pimavanserin and 93% for placebo; any serious adverse event: 17% for pimavanserin and 11% for placebo; any serious adverse event causing discontinuation: 9% for pimavanserin and 12% for placebo; weight loss of ≥7%: 15% for pimavanserin and 2% for placebo; QTc change: 9.5 ms for pimavanserin and −2 ms for placebo

continued

TABLE 2, *continued*

Category, Authors, Year	Study Type	Study Features	Outcomes
Brexpiprazole			
Grossberg et al., 2020 (41)	2 RCTs	Brexpiprazole vs. placebo	In study 1, the incidence of TEAEs over 12 weeks was 65.0% for brexpiprazole 2 mg/day, 49.0% for brexpiprazole 0.5–1 mg/day, and 45.9% for placebo; TEAEs with incidence ≥5% among patients receiving brexpiprazole 2 mg/day were headache (9.3% vs. 8.1% with placebo), insomnia (5.7% vs. 4.4%), dizziness (5.7% vs. 3.0%), and urinary tract infection (5.0% vs. 1.5%); among patients receiving brexpiprazole 0.5–1 mg/day, headache (7.6%); the rate discontinuation due to TEAEs was 4.3% for brexpiprazole 2 mg/day, 8.9% for brexpiprazole 0.5–1 mg/day, and 5.2% for placebo In study 2, the incidence of TEAEs over 12 weeks was 56.8% for brexpiprazole 0.5–2 mg/day and 58.4% for placebo; TEAEs with incidence ≥5% among patients receiving brexpiprazole 0.5–2 mg/day were headache (7.6% vs. 12.4% with placebo) and somnolence (6.1% vs. 3.6%); the incidence of serious TEAEs was 5.3% for brexpiprazole 0.5–2 mg/day and 4.4% for placebo; the rate of discontinuation due to TEAEs was 6.8% for brexpiprazole 0.5–2 mg/day and 0.7% for placebo
Combined adverse effects reported in meta-analyses			
Ballard and Waite, 2006 (32)	16 RCTs	AD; atypical antipsychotics vs. placebo; one atypical antipsychotic medication vs. other atypical antipsychotic medications	Risperidone vs. placebo: compared with the placebo group, the risperidone group had more adverse effects (1 mg/day: OR=1.43, p=0.05; 2 mg/day: OR=1.94, p=0.005), somnolence (1 mg/day: OR=2.38, p=<0.00001; 2 mg/day: OR=4.46, p<0.00001), urinary tract infection (2 mg/day: OR=1.82, p=0.05), upper respiratory infection (1 mg/day: OR=2.93, p=0.03), EPS (1 mg/day: OR=1.78, p=0.05), gait abnormality (1 mg/day: OR=5.31, p=0.0002), asthenia (1 mg/day: OR=4.37, p=0.05), and CVAEs (all dosages pooled: OR=3.64, p=0.0007) Risperidone 2 mg/day vs. 1 mg/day: compared with the 1 mg/day group, the 2 mg/day group had more dropouts (OR=1.65, p=0.04), falls (OR=2.24, p=0.008), EPS (OR=1.83, p=0.05), and pain (OR=1.90, p=0.02) Olanzapine vs. placebo: compared to the placebo group, the olanzapine group had more dropouts due to adverse effects (OR=3.34, p=0.0005), abnormal gait (5–10 mg/day: OR=9.41, p=0.03; >10 mg/day: OR=9.41, p=0.04), somnolence (5–10 mg/day: OR=3.72, p=0.000; >10 mg/day: OR=8.20, p=0.001), fever (OR=4.55, p=0.04), and urinary incontinence (OR=9.6, p=0.03) Aripiprazole vs. placebo: compared to the placebo group, the aripiprazole group had more somnolence (OR=8.24, p=0.05) Quetiapine: compared to the placebo group, cognition was worse in the quetiapine 50–100 mg/day group (p=0.01)
Schneider et al., 2006 (34)	15 RCTs	Dementia; atypical antipsychotics vs. placebo	Somnolence: drug-treated group compared to placebo group, OR=2.84; olanzapine group compared to aripiprazole and placebo groups, RD=0.16 vs. 0.06 EPS: drug-treated group compared to placebo group, OR=1.51; highest risk for EPS was in the risperidone group compared to the placebo group, OR=1.8 and RD=0.06; abnormal gait: risperidone and olanzapine groups compared to the placebo group, OR=3.42; edema: risperidone and olanzapine groups compared to placebo group, OR=1.99; urinary tract infections and urinary incontinence: drug-treated group compared to placebo group, OR=1.51; CVAEs: drug-treated group compared to placebo group, OR=2.13; higher in the risperidone group compared to the placebo group (OR=3.43)
Katz et al., 2007 (80)	4 RCTs	AD; risperidone vs. placebo	Somnolence: 18% in risperidone group, compared to 8% in placebo group; EPS: 12% in risperidone group, compared to 6% in placebo group; CVAEs: 1.6% in risperidone group, compared to 0.8% in placebo group; deaths within 30 days of the last dose: 3.1% in risperidone group, compared to 1.8% in placebo group (not statistically significant); no association between all-cause mortality and severity of behavioral symptoms at baseline

continued

TABLE 2, *continued*

Category, Authors, Year	Study Type	Study Features	Outcomes
Maher et al., 2011 (82)	18 RCTs	Dementia; atypical antipsychotics vs. placebo	CVAEs: olanzapine and risperidone groups compared to placebo group, ORs were 2.30 and 2.10, respectively; CVA: risperidone group compared to placebo group, OR=3.12; increased appetite and weight gain: olanzapine and risperidone groups compared to placebo group, pooled ORs were 4.70 and 3.40, respectively, and NNH was 25; anticholinergic effects: olanzapine group compared to placebo group, OR=3.30 and NNH=6; sedation and fatigue: olanzapine, quetiapine, and risperidone groups compared to placebo group, ORs were 4.60, 5.20, and 2.30, respectively; EPS: olanzapine and risperidone groups compared to placebo group, ORs were 15.20 and 3.00, respectively, and NNHs were 10 and 20, respectively; urinary tract symptoms: olanzapine, quetiapine, and risperidone groups compared to placebo group, ORs were 9.5, 2.4, and 1.6, respectively, and NNH was 16–36 Six head-to-head trials indicated that olanzapine use caused more neurological symptoms, including confusion, dizziness, headaches, etc., compared to risperidone use (OR=1.54)
Ma et al., 2014 (83)	16 RCTs	Dementia; atypical antipsychotics vs. placebo	EPS: drug-treated group (15.2%) compared to placebo group (8.6%), OR=1.74; risk higher in the olanzapine and risperidone groups; somnolence: drug-treated group (17%) compared to placebo group (7.2%), OR=2.95; risk higher in the aripiprazole, olanzapine, quetiapine, and risperidone groups; CVAEs: drug-treated group (2.1%) compared to placebo group (0.9%), OR=2.50; gait abnormality: drug-treated group (6.9%) compared to placebo group (1.7%), OR=1.74; risk higher in the olanzapine and risperidone groups; deaths within 30 days of drug discontinuation: drug-treated group (3.6%) compared to placebo group (2.3%), OR=1.5; subgroup meta-analyses did not identify any higher risk of death among the aripiprazole, olanzapine, quetiapine, or risperidone groups; edema: drug-treated group (9.3%) compared to placebo group (5.2%), OR=1.8; urinary tract infection: drug-treated group (14.9%) compared to placebo group (10.9%), OR=1.35; falls: drug-treated group (15.2%) compared to placebo group (18.8%)
Wang et al., 2015 (84)	6 RCTs	AD; atypical antipsychotics vs. placebo	Adverse effects: atypical antipsychotic group compared to placebo group, RR=1.17; dropout due to adverse events: atypical antipsychotic group compared to the placebo group, RR=2.24

[a] AD=Alzheimer's disease; aHR=adjusted hazard ratio; BPRS=Brief Psychiatric Rating Scale; CVA=cerebrovascular accident; CVAE=cardiovascular adverse event; EPS=extrapyramidal symptoms; HR=hazard ratio; LBD=Lewy body dementia; MMSE=Mini-Mental State Examination; NMA=network meta-analysis; NNH=number needed to harm; OR=odds ratio; QTc=corrected QT interval; RCT=randomized controlled trial; RR=relative risk or risk ratio; SMD=standardized mean difference; TEAE=treatment-emergent adverse events; WMD=weighted mean difference.

not always result in a worsening of NPS. In contrast, another meta-analysis of nine randomized controlled trials (55) reported that in the antipsychotic withdrawal group, a significantly greater proportion of individuals experienced a worsening of NPS. In a recent phase 3, double-blind, randomized, placebo-controlled discontinuation trial (56) that included individuals with psychosis related to AD, Parkinson's disease, Lewy body dementia, frontotemporal dementia, or vascular dementia, in patients with NPS who had responded to pimavanserin, a switch to placebo resulted in a greater likelihood of recurrence of psychosis compared to those continued on pimavanserin. There were no significant differences in the rates of adverse effects between participants continued on pimavanserin and those switched to placebo.

Summary

Based on clinical trial data, atypical antipsychotics have only modest efficacy in treating NPS in dementia patients. They have a significant risk of serious adverse events, including death, stroke, and cognitive decline. No consistent differences in efficacy or safety of different atypical antipsychotics have been demonstrated. Findings are mixed regarding worsening of NPS following antipsychotic withdrawal.

OTHER PHARMACOLOGICAL AND BIOLOGICAL TREATMENT MODALITIES

Acetylcholinesterase Inhibitors

A meta-analysis of 29 randomized controlled trials (57) showed that individuals who received acetylcholinesterase inhibitors did better on the NPI by a mean 1.72 points compared to individuals receiving placebo, a statistically significant but small benefit. There were no differences among donepezil, rivastigmine, and galantamine in terms of improvements on the NPI when compared to placebo. Tolerability data were not included.

TABLE 3. Studies of withdrawal of antipsychotics in patients with neuropsychiatric symptoms of dementia (NPS)[a]

Author, Year	Study Type	Outcomes
Declercq et al., 2013 (53)	9 trials, dementia; antipsychotic withdrawal vs. antipsychotic continuation	Eight of nine trials reported no overall difference between groups on withdrawal (remaining in study off antipsychotics) and NPS In one trial, time to relapse was reduced among the withdrawal group compared to the continuation group (p=0.04) In a second trial, in the first 16 weeks, rates of relapse were higher in the placebo group compared to the antipsychotic group (HR=1.94, p=0.004); in the next 16 weeks, rates of relapse were higher in the antipsychotic withdrawal group compared to the continuation group (HR=4.88, p=0.02) In two trials, individuals with more severe baseline NPS had a worsening of symptoms in the withdrawal group compared to the continuation group (p=0.009)
Pan et al., 2014 (55)	9 trials, dementia; antipsychotic withdrawal vs. antipsychotic continuation	NPS symptoms worsened more in the antipsychotic withdrawal group compared to the continuation group, but the difference did not reach statistical significance (SMD=0.19) A greater proportion of individuals had worsening of NPS in the antipsychotic withdrawal group compared to the continuation group (RR=1.78) A greater proportion of individuals had early study terminations in the antipsychotic withdrawal group compared to the continuation group, but the difference did not reach statistical significance (RR=1.11) A lower proportion of individuals died during the study period in the antipsychotic withdrawal group compared to the continuation group, but the difference did not reach statistical significance (RR=0.83)
Tariot et al., 2021 (56)	RCT	Among 217 individuals who had sustained response to pimavanserin, 105 were assigned to receive pimavanserin and 112 to receive placebo; relapse rates were 13% for the pimavanserin group and 28% for the placebo group (HR=0.35, p=0.005); adverse effects were reported in 41% of the pimavanserin group and 36% of the placebo group

[a] HR=hazard ratio; RCT=randomized controlled trial; RR=relative risk or risk ratio; SMD=standardized mean difference.

Memantine

A meta-analysis of six randomized controlled trials (58) found that individuals receiving memantine improved by 1.99 points on the NPI compared to those who received placebo, a significant but small benefit. Tolerability data were not included.

Antidepressants

A meta-analysis of two trials (59) reported that patients receiving sertraline and fluoxetine did significantly better on the CMAI than patients who received placebo (mean difference=−0.89; test for overall effect [Z]=5.32). The antidepressants were well tolerated, with no difference in rates of withdrawal due to adverse effects (relative risk=1.07).

Mood Stabilizers

A meta-analysis of five studies (60) found that among patients with AD, valproate/divalproex, carbamazepine, and lithium significantly worsened NPI total score (weighted mean difference=−0.89) and MMSE score (weighted mean difference=3.71) compared to placebo. There was no effect of the mood stabilizers compared to placebo on BPRS total score (weighted mean difference=0.83), CMAI total score (weighted mean difference=5.09), or NPI/BPRS agitation subscale score (SMD=0.30). A meta-analysis of two studies reported no difference between valproate and placebo on total BPRS score after 6 weeks of treatment (mean difference=0.23), and a meta-analysis of three studies of divalproex sodium found higher rates of adverse effects compared to placebo (odds ratio=2.02) (61).

Cannabinoids

A meta-analysis of three studies of tetrahydrocannabinol for NPS, five of dronabinol, and one of nabilone (62) showed benefits for the cannabinoids on the CMAI (SMD=−0.80), NPI total score (SMD=−0.61), NPI agitation/aggression subscore (SMD=−0.61), and nocturnal motor activity (SMD=−1.05). On meta-regressions and subgroup analyses, a larger effect size was noted for the CMAI among individuals with higher baseline MMSE scores. For the NPI total score, larger effect sizes were noted for higher total daily doses of cannabinoids. The only adverse effect was lethargy. There were no reports of serious adverse events.

A meta-analysis of four trials (63) did not find any significant benefit for cannabinoids (delta-9-tetrahydrocannabinol [THC] and two types of synthetic THC analogues [dronabinol and nabilone]) compared to placebo on the NPI/NPI-NH (mean difference=−1.97). There was also no difference in the number of adverse effects, except for sedation/lethargy with nabilone compared to placebo (odds ratio=2.83).

Repetitive Transcranial Magnetic Stimulation

A meta-analysis of two studies of rTMS in individuals with NPS (64) reported significant benefit for rTMS (overall effect=−0.58; test for overall effect [Z]=2.57). Minor tiredness was the only adverse effect noted.

Electroconvulsive Therapy (ECT)

As there have been no meta-analyses of ECT for NPS, we reviewed the data from two reviews. A systematic review of 17 studies (65) showed significant clinical improvement with ECT in 88% of the patients with NPS, especially on agitation, aggression, yelling/screaming, and food intake. Time to relapse of symptoms varied between 2 weeks and 7 months. Of the initial responders, 48% were referred for maintenance ECT. Adverse effects were mild and transient, and severe adverse effects (delirium, severe postictal confusion, and seizure) were uncommon (≤5%).

Tampi and colleagues' literature review (66) found 20 published reports on the use of ECT for NPS, including 172 individuals, mostly with dementia: AD (40%), vascular dementia (13%), or unspecified dementia (15%). Positive response to ECT was noted in >90% of patients with physical aggression and suicidal behaviors. Adverse effects were mild and transient; postictal confusion/memory impairment was the most common adverse effect, seen in 15% of the individuals.

Summary

Acetylcholinesterase inhibitors, memantine, and antidepressants produce small improvements in NPS, and mood stabilizers are ineffective. The literature on rTMS and ECT is too limited to draw conclusions.

PREVENTION OF DEMENTIA AND NPS

A recent review identified 12 modifiable risk factors for dementia: lower levels of education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, excessive alcohol consumption, traumatic brain injury, air pollution, and infrequent social contact (67). These risk factors account for around 40% cases of dementia worldwide, and can potentially be modified. There has also been a call by various experts to try to prevent the onset of NPS (68, 69). Person-centered care is a framework in which health practitioners and persons with dementia and their caregivers work collaboratively to tailor the care to meet each individual's needs (70). The person-centered care framework improves outcomes for dementia patients by promoting a positive social environment, a healthier lifestyle, and adherence to treatment. There is some evidence to suggest that the person-centered care approach can be successful in preventing NPS and reducing antipsychotic use (68, 71). This includes a range of sensory practices (e.g., bright light therapy), psychosocial practices (e.g., reminiscence therapy, music therapy, pet therapy), and structured care protocols (e.g., mouth and bath care) that can reduce the risk of NPS and manage them when they occur (71). Additionally, structured protocols like the DICE can lead to greater efficiency and precision in the assessment of individuals with NPS and improve the quality of their care (72).

There are five classes of strategies for prevention of dementia and NPS to reduce their incidence and progression (73). Prevention can be categorized as primordial (preventing risk factors like head injuries), primary (treating major depression to reduce risk of developing dementia), secondary (educating caregivers about NPS), tertiary (using person-centered care and DICE to prevent inappropriate treatment of individuals with NPS), and quaternary (avoiding anticholinergic delirium due to polypharmacy).

CLINICAL PRACTICE GUIDELINES

Given that moderate to severe cognitive impairment is a pathognomonic feature of dementia, it is necessary to confirm a dementia patient's capacity to consent when prescribing antipsychotics or other treatments that carry a significant risk of serious adverse events (74). Age, education, and severity of cognitive deficits are predictors of decision-making capacity. Brief, pragmatic, and validated measures to assess this capacity are available and should be used (75).

Published studies and guidelines suggest nonpharmacological management of NPS as first-line management. However, lack of adequate caregiver training and problems in implementation often lead to the use of pharmacotherapy in dementia patients. A systematic approach to assessment, evidence-based medication and dosage selection, monitoring, and appropriate documentation would facilitate improvement (76, 77). There should be a clear documentation of the risks and benefits for the prescribed treatment for the individual patient with NPS. When a medication is prescribed, persistence of symptoms should be evaluated regularly to consider dosage changes and possible discontinuation while avoiding recurrence or worsening of NPS.

Available evidence indicates that atypical antipsychotics have shown modest efficacy in the treatment of symptoms of NPS, including psychosis, aggression, agitation, anxiety, and euphoria (32–34, 36–41, 78–85). These drugs appear to provide short-term benefit in the treatment of NPS, but their long-term benefit is unclear. There is no clear evidence for the superiority for any individual drugs over others. Serious adverse effects, including greater risk for death, CVAEs, and cognitive decline (52, 66), appear to be a class effect rather than an individual drug effect. These adverse effects are more common when higher dosages are used and for longer time periods.

Based on the available evidence, atypical antipsychotics should be used in individuals with NPS only when the symptoms are either severe or refractory and where nonpharmacological and other treatments have failed to produce benefit or are not safe or feasible to use (86). Even in such situations, atypical antipsychotics should be used at the lowest effective dosage and for the shortest possible time, with close monitoring of risk factors and adverse effects (76). Additionally, clinicians should follow national guidelines such as the APA practice guideline (Box 1) and the European Academy of Neurology guidelines when prescribing medications for patients with NPS (70, 87).

BOX 1. Salient aspects of the APA practice guideline on using antipsychotics for neuropsychiatric symptoms of dementia (NPS)[a]

- The guideline recommends a risk and benefit analysis prior to prescribing antipsychotics for individuals with NPS.
- A dementia patient's decision-making capacity should be assessed.
- If the risk-benefit analysis favors the use of antipsychotics in an individual with NPS, then treatment should be initiated at the lowest possible dosage of an antipsychotic medication and titrated up to the minimum effective dosage as tolerated.
- If an individual with NPS experiences clinically significant adverse effects from the medication, the potential risks versus benefits of using the medication should be reevaluated.
- If there is no noticeable benefit from the medication after a 4-week trial at an adequate dosage, then the medication should be tapered and discontinued.
- If there is a positive response to the medication trial, an attempt to taper and withdraw the medication should be made within 4 months of initiation of treatment after discussions with the patient and/or their surrogate decision maker. The only reason a taper would not be possible is if the individual has experienced a significant recurrence of symptoms with previous trials of tapering the medication.
- While the medication taper is being attempted, the patient should be evaluated monthly for at least 4 months after the medication has been discontinued to identify signs of recurrence of NPS.
- In the absence of delirium, haloperidol should not be used as a first-line agent for managing nonemergent NPS.
- Individuals with NPS should not receive long-acting injectable antipsychotic medications unless they have a comorbid chronic psychotic illness.

[a] From the APA Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients With Dementia (87).

FUTURE RESEARCH DIRECTIONS

Research on the neurobiology of NPS needs to be expanded, as it may unearth novel therapeutic targets. Studies with molecular imaging, genetics, and use of biomarkers of inflammation as well as amyloid and tau could provide new insights. Nonpharmacological treatments, including person-centered care, have benefits with small to medium effect sizes and are generally feasible and should be considered first-line treatments for NPS. The majority of the trials of pharmacotherapeutic agents have been conducted in individuals with AD. Future trials should include individuals with other types of dementias, including vascular dementia, Lewy body dementia, and frontotemporal dementia, to evaluate the agents' efficacy and tolerability among these groups. There is also limited evidence that cannabinoids, rTMS, and ECT may be beneficial for some individuals with NPS (62–66). Randomized controlled trials with adequate power to detect treatment effects should be conducted with these different modalities to identify their definitive role in the management of NPS. It would also be interesting to evaluate the effect of amyloid-targeting drugs among individuals with AD who develop NPS (88). Additionally, pharmacogenetic trials among individuals with NPS might yield interesting data that could help clinicians choose specific medications to treat NPS (89). Furthermore, investing in controlled trials of prevention strategies for NPS would be highly beneficial in improving the care of these individuals and helping their caregivers.

The use of technology in clinical practice, including telepsychiatry, has been growing rapidly, spurred by the COVID-19 pandemic and the physical isolation necessary to reduce the spread of infection. There is some evidence that use of devices like tablets can help reduce agitation in dementia patients (90). Randomized controlled trials using technologies such as smartphones, tablets, virtual reality, and wearable sensors could be useful in subgroups of patients with NPS.

CONCLUSIONS

Atypical antipsychotics should be used cautiously (with the lowest effective dosage and for the shortest duration possible) in individuals with NPS, and only when symptoms have not responded adequately to nonpharmacological strategies. The use of person-centered care and other nonpharmacological treatments, either as stand-alone treatments or in combination with appropriate medications, may help reduce the incidence and duration of the use of these medications. Regular risk-benefit analysis should be conducted when using different treatments to maximize gains and minimize adverse outcomes.

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