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Management of cognitive and negative symptoms in schizophrenia

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Abstract

Currently available antipsychotics provide only modest benefit in managing the cognitive and negative symptoms of schizophrenia even though these symptoms are often the most impairing in patients' daily lives. Certain antipsychotics may have slight benefits over others, and several nonpharmacologic and pharmacologic adjunctive treatments have been evaluated in recent clinical trials. Recently published meta-analyses and clinical studies of such treatments are reviewed. Potential strategies to manage cognitive and negative symptoms, including deprescribing of medications that may exacerbate these symptoms, are described using theoretical case examples.

Keywords: negative symptoms, cognitive symptoms, schizophrenia, antipsychotics, anticholinergic

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Introduction

Despite the number of antipsychotic medication options available for the treatment of schizophrenia, management of cognitive and negative symptoms is a largely unmet clinical need. Negative symptoms, such as alogia, avolition, and affective flattening, are prominent in an estimated 40% of patients with schizophrenia while cognitive symptoms, such as difficulties with attention or working memory, are prominent in up to 80% of patients.[1] These symptoms are highly correlated with functional outcomes, such as psychosocial functioning, employment, and quality of life.[1,2] There are currently no FDA-approved treatment options for management of cognitive and negative symptoms of schizophrenia although there are medications in phase II and phase III trials in the pipeline.[3-5]

When evaluating patients with cognitive and negative symptoms, it is important to distinguish between primary versus secondary symptoms. Secondary causes of symptoms, such as comorbid conditions (eg, depression, dementia, substance use disorder) or adverse effects of medications (eg, sedation or extrapyramidal symptoms [EPS]) should be investigated and addressed accordingly.[1] Additionally, negative and cognitive symptoms are thought to be closely related and may reinforce each other. For example, impaired executive functioning may lead to decreased goal-directed behavior, resulting in avolition, or memory impairment may contribute to alogia.[6] Patients typically do not spontaneously report cognitive and negative symptoms due to lack of awareness; therefore, observing the patient during clinical interview as well as gathering information from caregivers is important in assessing for such symptoms.[1] Rating scales, such as the Scale for the Assessment of Negative Symptoms,

negative symptom subscale of the PANSS, Brief Assessment of Cognition in Schizophrenia (BACS), and Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB), have been developed but are typically only used in the context of clinical trials.[1,7] Negative symptoms are sometimes further categorized using the terms "persistent" (moderate-severe symptoms persisting for at least 6 months), "prominent" (presence of moderate-severe negative symptoms), or "predominant" (presence of moderate-severe negative symptoms with fewer or less severe positive symptoms).[2]

This article reviews the most recent, clinically pertinent data on the nonpharmacologic and pharmacologic management of negative and cognitive symptoms of schizophrenia, also known as cognitive impairment associated with schizophrenia (CIAS), and highlight the selection of appropriate treatment options through the use of illustrative case examples.

Case 1: CIAS

A.D. is a 32-year-old patient with a long-standing history of schizophrenia who presents to an outpatient psychiatrist appointment endorsing difficulty focusing and forgetfulness. The patient was recently able to obtain a part-time job at a hardware store and attends a day program 3 days per week. Since starting the job, A.D. reports forgetting to complete tasks at work and getting distracted while driving, resulting in an accident a few weeks ago. Positive symptoms have been stable for the past 2 years on a combination of aripiprazole lauroxil 662 mg IM monthly and clozapine 200 mg daily at bedtime. Prior to this, the patient had been tried on several medication regimens, including clozapine monotherapy at a dose of 400 mg/d; however, this caused excessive sedation at this dose. The patient has a history of experiencing frequent relapses in psychotic symptoms, including paranoia and auditory hallucinations, but denies any current psychosis. A.D. decreased caffeine intake and frequency of vaping nicotine usage and asks if this recent decrease in use may be contributing to these cognitive difficulties. A mental status exam noted appropriate grooming, neutral mood and affect, and a linear thought process but poor attention and short-term memory.

Several psychosocial treatments have been studied for the treatment of CIAS with the most positive effects seen with cognitive remediation therapy (CRT).[8,9] The American Psychiatric Association (APA) schizophrenia treatment guideline suggests the use of CRT but notes that this treatment modality may not be widely available.[10] Additional nonpharmacologic treatments that show benefit in measures of cognition include compensatory interventions, physical exercise (mainly aerobic exercise), and transcranial direct current stimulation.[7,11] A summary of notable literature for nonpharmacologic and pharmacologic interventions for cognitive symptoms of schizophrenia appears in Table 1.[8,9,11-35] Systematic reviews and meta-analyses are included when available along with any subsequently published randomized controlled trials (RCTs). Commercially available interventions that have been studied in at least 2 RCTs are included. A recent meta-analysis[15] of four RCTs comparing second generation antipsychotics (SGAs) to placebo found a small effect size of 0.22 on measures of cognitive function.[15]

Baldez et al[14] performed network meta-analyses on studies of antipsychotic effects on measures of cognitive performance across 9 domains. The authors found that amisulpride, lurasidone, olanzapine, perphenazine, quetiapine, risperidone, and ziprasidone had potentially positive effects on cognition, but effects were not consistent across all domains. They also found that haloperidol had consistently negative effects on cognition. Previously conducted meta-analyses and large pragmatic trials,[36-39] such as the Clinical Antipsychotic Trials of Intervention Effectiveness[38] (which was included in the Baldez meta-analyses), and Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia trial[39]

Take Home Points:

1. Second generation antipsychotics may be preferable to first generation antipsychotics in patients with cognitive impairment associated with schizophrenia (CIAS), although data is mixed. The most promising adjunctive interventions for the management of CIAS include cognitive remediation, physical exercise, buspirone, memantine, N-acetylcysteine, and ondansetron although additional well-designed studies are necessary.
2. Amisulpride, cariprazine, and clozapine may exert more clinical benefit in the management of negative symptoms than other antipsychotics; however, clozapine may only be more effective in managing negative symptoms secondary to positive symptom improvement. Possibly effective adjunctive treatments for negative symptoms include social skills training, physical exercise, memantine, minocycline, N-acetylcysteine, pimavanserin, raloxifene/estrogen, and selective serotonin reuptake inhibitors.
3. Medications that may worsen or cause secondary negative or cognitive symptoms include sedating antipsychotics, benzodiazepines, and anticholinergic medications. Long-term use of anticholinergic medications, such as benztropine and trihexyphenidyl, is controversial. Many patients may benefit from deprescribing of these agents. Amantadine may be a suitable alternative for managing antipsychotic-induced parkinsonism when necessary.

TABLE 1: Clinical studies of interventions for cognitive impairment associated with schizophrenia (CIAS)

Nonpharmacologic Interventions			
Intervention	**Studies**	**Study Results**	**Conclusions**
Cognitive remediation therapy (CRT)	• Meta-analysis[8] of 73 RCTs (n = 4594) published between 1980 and May 2020 • Meta-analysis[9] of 130 RCTs (n = 8851) published up until Feb 2020	• Global cognition effect size = 0.29 in both meta-analyses • Effect sizes for specific cognitive domains ranged from 0.17 (attention) to 0.33 (verbal learning) • Functional outcomes effect size = 0.21 to 0.22 • Negative symptoms effect size = 0.14 to 0.16 • Interventions that included a trained therapist and structured psychiatric rehabilitation were significantly more effective	• CRT has a small-moderate effect on measures of cognition, with the greatest effect on verbal learning • Effects on functional outcomes and negative symptoms are small • CRT should include a trained therapist and be combined with psychiatric rehabilitation for optimal outcomes
Cognitive compensatory interventions	Meta-analysis[11] of 26 RCTs (n = 1654) published up until Oct 18, 2018	• Interventions included external strategies/ environmental modification, internal self-management strategies, and errorless learning • Overall functional outcomes effect size (Hedge g) = 0.46 (95% CI = 0.33, 0.6, $P < .001$) • Effects were durable over a median of 6 months • Longer interventions associated with larger effects ($z = 2.11$, $P = .04$)	• Cognitive compensatory interventions produce a moderate effect on functional outcomes • These interventions can be used alone or in combination with CRT or other interventions
Physical exercise	Meta-analysis[12] of 10 controlled trials (n = 383) published up until Apr 2016	• Interventions mostly focused on aerobic exercise (eg, brisk walking or jogging) with 3 studies also including resistance-based training • Global cognition effect size (Hedge g) = 0.33 • Significant effects seen in 3 out of 7 domains: working memory (Hedge g = 0.39), attention/vigilance (0.66), and social cognition (0.71) • Interventions that included supervision by a physical activity professional were significantly effective (Hedge g = 0.47, $P < .001$), whereas those supervised by mental health or research staff were not	• Exercise produces a moderate effect on overall cognition with large effects on measures of attention/ vigilance and social cognition • Patients should ideally be supervised by a trained professional, such as a physical trainer or yoga instructor
Transcranial direct current stimulation (tDCS)	Review[13] of 6 randomized sham-controlled studies published through May 2016	• Mean effect of anodal stimulation on general cognitive ability across 3 studies = 0.2 (95% CI = –0.37, –0.76) • No statistically significant benefits found in 6 studies reviewed	• tDCS does not appear to be beneficial in CIAS although more studies may be needed

have had conflicting results regarding superiority of individual antipsychotics.

A direct comparison of first generation antipsychotics (FGAs) and SGAs in the Neuroleptic Strategy Study was published in 2019.[16] In this trial, patients were randomized to treatment with either an FGA (haloperidol or flupenthixol) or SGA (olanzapine, aripiprazole, or quetiapine) for a total of 24 weeks and were assessed using a neurocognitive test battery. A total of 114 subjects were included in the statistical analysis (52 in the FGA group and 62 in the SGA group). Patients treated with FGAs showed no statistically significant change in global cognition during the trial, whereas patients treated with SGAs had a statistically

TABLE 1: Clinical studies of interventions for cognitive impairment associated with schizophrenia (CIAS) (continued)

Pharmacologic Interventions

Intervention	Studies	Study Results	Conclusions
Antipsychotics	• Network meta-analyses[14] of 54 double-blind RCTs (n = 5866) published through Nov 30, 2018 • Meta-analysis[15] of 4 placebo-controlled RCTs (n = 1231) published between May 18, 2016 and Oct 15, 2019 • 24-wk double-blind[16] RCT of FGAs (haloperidol or flupentixol) vs SGAs (aripiprazole, olanzapine, quetiapine; n = 114)	• SGAs global composite cognitive score effect size = 0.22 to 0.24 • FGAs had no significant benefit and in 1 study showed decline in cognition over time • One meta-analysis ranked medications based on SUCRA[a] of the cognitive composite score as follows: lurasidone (0.85) > amisulpride (0.81) > perphenazine (0.79) > ziprasidone (0.6) > quetiapine (0.54) > olanzapine (0.5) > risperidone (0.38) > placebo (0.25) > clozapine (0.16) > haloperidol (0.11) • On individual measures, amisulpride performed the best on measures of attention and verbal memory, and haloperidol performed the worst in all cognitive domains • Longer duration of treatment (at least 3 mo) was associated with greater improvement in cognitive outcomes in 1 meta-analysis (P = .044)	• Overall, the effects of antipsychotics on CIAS are small • SGAs are generally superior to FGAs • Amisulpride may have a small benefit over other antipsychotics; however. it is not available in the United States • Cognitive benefits with SGAs may take several months

Adjunctive Pharmacologic Interventions

Intervention	Studies	Study Results	Conclusions
Cognitive enhancers from various neurotransmitter systems	Meta-analysis[17] of 93 double-blind RCTs (n = 5630) published between 1998 and 2017	• Pooled analysis of all interventions Hedge g effect size = 0.1 (95% CI = 0.01, 0.18) • Glutamatergic medications effect size = 0.19 (95% CI = 0.04, 0.34) • Cholinergic medications overall showed no benefit, effect size = 0.077 (95% CI = –0.04, 0.2) • AChE inhibitors no effect on overall function, but on working memory effect size = 0.26 (95% CI = 0.02, 0.5) • No significant effects found for serotonergic, dopaminergic, GABA-ergic, or noradrenergic medications • Heterogeneity was considered low-moderate	• So-called cognitive enhancing medications have very limited benefit on CIAS overall • Medications affecting glutamate have the most promise, but many of the included studies were underpowered

significant improvement in global cognition from baseline to week 6 (P = .037), but effects were nonsignificant through week 24. The authors noted that the magnitude of benefit was small and the results may be due to attenuated adverse effects of SGAs compared with FGAs as opposed to true procognitive effects. There were minimal differences between the individual SGAs studied.[16] Overall, it appears that differences between the antipsychotics are small; however, SGAs may be preferred over FGAs.

In the case of clozapine, lower clozapine to N-desmethyl-clozapine (NDMC) plasma concentration ratios are associated with better cognitive functioning in several observational studies, possibly due to a differential effect of the parent drug and its metabolite on muscarinic receptors.[40-44] However, these findings have not been universally consistent.[45] Furthermore, clozapine:NDMC plasma ratios may not currently be reliable enough for clinical decision making.[46] Of note, a formulation of NDMC

TABLE 1: Clinical studies of interventions for cognitive impairment associated with schizophrenia (CIAS) (continued)

Adjunctive Pharmacologic Interventions			
Intervention	**Studies**	**Study Results**	**Conclusions**
Anti-dementia drugs (AChE inhibitors, memantine)	• Meta-analysis[18] of 9 RCTS (n = 348) published up until Mar 2018 • Meta-analysis[19] of 37 double-blind RCTs (n = 1574) published up until Jan 6, 2018	• One meta-analysis showed significant improvement in MMSE scores overall (SMD = –0.79[b]; 95% CI = –1.23, –0.34; P = .0006) with greater effects associated with younger age of the patient (P = .003) • Memantine (20 mg/d) had the largest effect size of the medications studied (SMD = –1.05; 95% CI = –1.59, –0.51; P = .0001) • AChE inhibitors showed a moderate effect on processing speed (SMD = –0.52; 95% CI = –0.79, –0.25; P = 0.0002), small-moderate effect on attention (SMD = –0.43; 95% CI = –0.72, –0.13; P = .005), and no effect on working memory • No significant difference in other measures of cognition, including composite cognitive test scores	• Antidementia drugs may show improvement on MMSE scores, but this was not confirmed with other global measures of CIAS • Memantine (20 mg/d) has the most promising results
Anti-inflammatory medications	• Meta-analysis[20] of 14 RCTs (n = 468) published up until Aug 2017 • Meta-analysis[21] of 72 RCTs (n = 4104) published up until Feb 6, 2020	• One meta-analysis found significant cognitive benefits with minocycline 100 to 200 mg/d (Hedge g effect size = 0.21, 95% CI = 0.04, 0.38) and pregnenolone 30 to 500 mg/d (0.19, 95% CI = 0.08, 0.29) without significant adverse effects • No other significant differences found with other individual medications • A second meta-analysis found that anti-inflammatory treated patients overall had greater improvement in working memory (SMD = 0.21, 95% CI = 0.03, 0.40) but no significant effect on other measures of cognition	• Anti-inflammatory medications may produce a small benefit in CIAS • Minocycline and pregnenolone appear the most promising
Buspirone	• Review[22] of 4 RCTs (n = 216) published up until Apr 25, 2017 • 24-wk double-blind[23] RCT vs placebo; adjunctive to SGA (n = 196)	• Two studies of buspirone 30 mg/d vs placebo found improvement in cognitive measures: attention/speeded motor performance (1 study) and verbal and performance intelligence (1 study) • Another study of 30 mg/d saw significant improvement on total score (P = .002) and several domains of the WAIS-RC, including arithmetic (P = .034), similarities (P = .018), picture completion (P = .005) and block design (P = .006), as well as SDSS (P = .031) and FBIS (P = .016) • Two other placebo-controlled RCTs saw no improvement in measures of cognition • No significant difference in adverse effects between buspirone and placebo groups in the 3 studies that reported them	• Although evidence is mixed, buspirone 30 mg/d may offer some improvement in certain measures of cognition including attention, logical reasoning, and visual memory • Buspirone was well tolerated

was previously in development for CIAS, but it did not demonstrate efficacy in phase II trials.[47]

Several adjunctive treatments for CIAS have been investigated in recent years, but none has shown consistent benefit in clinical trials. Buspirone may improve cognitive function via stimulation of serotonin type 1A (5-HT1A) receptors in the prefrontal cortex.[22] Buspirone has been studied for CIAS in 5 RCTs. Of these, the 3 studies that were longer in duration (12 to 24 weeks) showed potential cognitive benefits, whereas

TABLE 1: Clinical studies of interventions for cognitive impairment associated with schizophrenia (CIAS) (continued)

Adjunctive Pharmacologic Interventions			
Intervention	**Studies**	**Study Results**	**Conclusions**
Memantine	• 8-wk double-blind[24] RCT vs placebo in patients with chronic stable schizophrenia (n = 44) • 24-wk double-blind[25] RCT vs placebo; adjunctive to risperidone (n = 19 acute schizophrenia, n = 16 chronic schizophrenia with predominant negative symptoms)	• See antidementia drug section for results from previous meta-analyses • A dose of 20 mg/d was employed in both studies • Improvements demonstrated in attention intensity ($P = .005$), verbal learning ($P = .05$), problem-solving ($P = .043$), and flexibility ($P = .049$) in patients with acute episode of schizophrenia • In 8-wk study of patients with chronic stable illness, improvements seen in verbal memory ($P = .01$), working memory ($P = .007$), and verbal fluency ($P = .013$) • In patients with stable positive symptoms and predominant negative symptoms, memantine showed significant improvement in immediate memory ($P = .033$), but no other significant benefits • Overall incidence of adverse effects was low	• Memantine 20 mg/d demonstrated statistically significant benefits on various measures of cognition using standardized assessment batteries, however sample sizes were small • Cognitive benefit may be less in patients with predominant negative symptoms • Memantine was well tolerated
Minocycline	• 16-wk double blind[26] RCT vs placebo (n = 200) • 12-wk double blind[27] RCT of minocycline 100 mg/d vs minocycline 200 mg/d vs placebo adjunctive to risperidone (n = 75)	• See anti-inflammatory section for results of meta-analysis • One study showed benefit for minocycline 200 mg/d in measures of speed information processing vs minocycline 100 mg/d and placebo ($P = .017$ for both) • Improvements were correlated with reductions in pro-inflammatory cytokines (IL-1B and IL-6) and remission of negative symptoms • Another placebo-controlled RCT saw no cognitive benefit • No significant differences in adverse effects between minocycline and placebo groups	• Although results are mixed, minocycline's anti-inflammatory effects may produce some benefit in CIAS • Improvements may be secondary to benefit in negative symptoms • Minocycline appears well tolerated
N-acetylcysteine (NAC)	• Review of 3 RCTs[28] (n = 154) published between 2008 and 2018 • 12-wk double blind[29] RCT vs placebo (n = 84) • 52-wk double blind[30] RCT vs placebo (n = 60)	• Doses ranged from 1200 to 3600 mg/d • Study duration ranged from 60 d to 52 wk • Improvements demonstrated vs placebo included MMSE score ($P < .001$) and measures of auditory cognitive processing ($P = .025$), working memory ($P = .027$), and processing speed ($P = .022$) in shorter term studies • No cognitive benefit seen in 52-wk study • Cognitive improvement was significantly correlated with negative symptom improvement in one study, but not in another study • Minimal side effects reported including mild abdominal cramping	• NAC demonstrated significant but inconsistent benefits in cognition • NAC is generally well tolerated and has been studied at longer durations than most other interventions (up to 1 y)

shorter term studies (6 weeks) did not. Two of the positive studies specifically looked at buspirone added adjunctively to risperidone, and the third study included several different SGAs. The mean dose in each of the positive trials was 30 mg/d.[22,23] Buspirone may be a favorable option for patients with comorbid anxiety or depressive disorders. Due to its relatively benign side effect profile, it could be recommended preferentially over other treatment options.

TABLE 1: Clinical studies of interventions for cognitive impairment associated with schizophrenia (CIAS) (continued)

Adjunctive Pharmacologic Interventions			
Intervention	**Studies**	**Study Results**	**Conclusions**
Ondansetron	Systematic review and meta-analysis[31] of 5 RCTs (n = 304) published up until Nov 1, 2018	• Two out of five RCTs found ondansetron to be superior to placebo in cognitive items of the PANSS at wk 12 ($P < .05$) • One study found improvements in visual memory ($P = .002$) and 1 in object assembly (effect size = 1.77, $P < .001$) and comprehension (effect size = 1.48, $P = .001$) • A dose of 8 mg once daily was most commonly studied • One study found improvement in severity of EPS as measured by ESRS versus placebo ($P = .001$) and in AIMS scale score versus placebo ($P = .01$) • No significant differences in adverse events	• Ondansetron 8 mg/d may provide some benefit in CIAS, although results are inconsistent • Ondansetron appears to be well tolerated and may possibly improve EPS symptoms
Raloxifene	• Meta-analysis[32] of 9 RCTs (n = 561) published up until Oct 10, 2017 • Pooled data[33] from 2 double blind RCTs (1 in women age 40 to 70 y, 1 in women age 18 to 45 y; n = 69) • 6-wk, double-blind, placebo-controlled RCT vs isradapine[34] (n = 64) • 24-wk double-blind, placebo-controlled RCT in postmenopausal women[35] (n = 68)	• Meta-analysis found no significant benefits in cognition • Dosing ranged from 60 to 120 mg/d • Two out of 3 subsequently published studies found significant benefit in verbal memory vs placebo (1 study; $P = .002$), verbal recognition (1 study; $P = .04$), and picture naming (1 study; $P = .04$) • One study found that measures of semantic fluency worsened with raloxifene vs placebo ($P = .005$) • No significant difference in adverse effects when reported	• Although results are inconsistent, overall raloxifene does not seem to have significant benefit in CIAS

AIMS = Abnormal Involuntary Movement Scale; CI = confidence interval; EPS = extrapyramidal symptoms; ESRS = Extrapyramidal Symptom Rating Scale; FBIS = Family Burden Interview Scale; FGA = first generation antipsychotic; IL = interleukin; MMSE = Mini Mental State Exam; RCT = randomized controlled trial; SDSS = Social Disability Screening Scale; SGA = second generation antipsychotic; SMD = standardized mean difference; SUCRA = surface area under the cumulative ranking curve; WAIS-RC = Wechsler Adult Intelligence Scale-Revised in China

[a]Treatments ordered according to the probability of being the best, second best, etc. A SUCRA value of 1 means that the treatment is 100% likely to be the best, and a value of 0 means that it is certainly the worst.

[b]Because lower scores on the MMSE indicate greater symptom severity, the authors reversed the algebraic sign of the numerical scores to report an improvement in symptoms.

Memantine, which has a well-established role in preserving cognition in patients with dementia, may also have benefit in schizophrenia, possibly due to its effects on glutamatergic signaling, 5-HT3 inhibition, and activity at nicotinic cholinergic receptors.[48] Whereas a previous systematic review[49] of open-label and double-blind trials of memantine concluded that there was no benefit in its use for CIAS, more recent trials and meta-analyses show some potential benefit.[24,25,50] In a 2018 meta-analysis of adjunctive antidementia drugs in schizophrenia, Kishi et al[19] found a statistically significant improvement in Mini-Mental State Examination (MMSE) scores with memantine 20 mg/d compared with adjunctive placebo. The authors did not, however, find a significant improvement in any other measures of cognition.[19] A separate meta-analysis of trials[51] of just memantine had similar results. A major limitation of these studies is that, whereas often used in studies of dementia, the MMSE may not accurately measure CIAS compared with other tools, such as the BACS or MATRICS.[48] Heterogeneity of the included studies also

limits the applicability of these findings to clinical practice. Memantine should be further evaluated before recommending its routine use in clinical practice for CIAS.

Minocycline has been proposed as a potential adjunctive treatment for CIAS due to its anti-inflammatory and glutamatergic enhancing effects.[52] One 12-week study showed improvements in measures of speed of information processing with minocycline 200 mg/d but not 100 mg/d[27] and a 16-week study in patients taking minocycline 200 mg/d adjunctively with risperidone saw improvement in measures of attention.[52] However, a larger 16-week study of minocycline 200 mg/d failed to show any cognitive benefit.[26] Given the mixed results to date and the potential for inducing antibiotic resistance, this should not be considered a first choice option for cognitive symptoms.

As a glutathione precursor, N-acetylcysteine (NAC) may reduce oxidative stress, resulting in improved cognition.[28] To date 60-day[28] and 12-week[29] and 24-week studies[53,54] of NAC 1200 to 2700 mg/d adjunctive to an antipsychotic showed statistically significant improvement in at least 1 measure of cognitive functioning, including the MMSE and measures of auditory cognitive processing, working memory, and processing speed, whereas a 52-week study[30] of 3600 mg/d did not show benefit. Adverse effects were not consistently reported, but those that were reported were mild, making it an attractive option.

As mentioned, 5-HT3 receptors are implicated in the pathogenesis of cognitive dysfunction in schizophrenia. A systematic review and meta-analysis of studies of ondansetron, a 5-HT3 antagonist, used adjunctively to antipsychotics in patients with schizophrenia included 5 RCTs that examined its effect on cognitive functioning. The methods used to assess cognitive functioning in these studies were too heterogeneous to allow for meta-analysis. Dosing ranged from 4 to 8 mg/d with 8 mg/d being most common. Two studies found improvement on the cognitive subscale of the PANSS, but 1 of these 2 trials found no benefit in any of the subdomains of the MCCB. A third study found benefit in measures of visual memory, and a fourth saw improvements in object assembly and comprehension. Two of the studies specifically studied ondansetron adjunctive to risperidone, 1 to haloperidol, and the others to various antipsychotics.[31] Ondansetron has a dose-dependent risk of QTc prolongation that needs to be considered in patients taking psychotropic medications that may prolong the QTc interval.[55] Given its otherwise benign adverse effect profile, although fatigue may be of concern, this may be a favorable option for most patients.

Sex hormones, particularly estrogen, show potential cognitive benefits in patients with schizophrenia.[56] The selective estrogen receptor modulator raloxifene has been studied in several studies for treatment of CIAS, mainly in women. Results of these studies are inconsistent.[57] A 2018 meta-analysis[32] of adjunctive raloxifene 60 to 120 mg/d found no significant cognitive benefits versus placebo. Subsequently published studies have had mixed results with 1 study[35] of 60 mg/d of raloxifene in postmenopausal women showing no benefit and another study[33] of 120 mg/d in women across the menopause spectrum showing improvements in some measures of cognition and worsening in others. Another study[34] of raloxifene 120 mg/d in both males and females demonstrated improvements in verbal memory. Similarly, the progesterone precursor pregnenolone has had inconsistent results in clinical studies of CIAS. In these trials, high serum pregnenolone concentrations at baseline were correlated with less improvement in cognitive function.[57] Given the significant warnings for thromboembolic events with raloxifene, these inconsistent benefits may be overshadowed by potential risk.

Case 1 Discussion

Given the described evidence and their relatively benign side effect profile, buspirone, NAC, or ondansetron may be suitable options to consider for A.D. Discussing these options with the patient using a shared decision-making approach would be appropriate. Given its once daily dosing, ondansetron may be preferred by the patient as opposed to NAC, which is typically dosed twice daily, or buspirone, which is typically dosed 2 to 3 times daily. Additionally, cognitive remediation should be offered, if available, as it is one of the few modalities that has consistently shown positive (albeit small) benefit in CIAS. Physical exercise should be encouraged, preferably in a structured setting with supervision from a trained professional. This may be particularly helpful in managing attention-related difficulties, which A.D. is experiencing. Finally, given A.D.'s perceived benefit of nicotine and caffeine on cognitive functioning, it may be tempting for A.D. to increase usage of these stimulants. Although caffeine may lessen sedation related to antipsychotics, it can also raise blood concentrations of clozapine, and cigarette smoking can decrease clozapine concentrations.[10] Monitoring the clozapine:NDMC ratio should be considered; however, it may not be clinically reliable. A discussion about the potential risks and lack of clinically confirmed benefits of nicotine and caffeine should be had with the patient.

Case 2: Negative Symptoms

P.M. is a 44-year-old patient currently in outpatient treatment for schizophrenia. The patient has a history of multiple hospitalizations for acute exacerbations of schizophrenia, the last being approximately 18 months ago. Since that time, P.M. has had significant improvement in paranoid thoughts and denies current hallucinations. P.M.

endorses having occasional thoughts that the police will come to arrest the patient but is able to recognize that these thoughts are unwarranted and does not find them bothersome. P.M. is currently taking iloperidone 12 mg once daily. Previous antipsychotic medication trials include brexpiprazole (sedation), ziprasidone (ineffective), perphenazine (EPS), and olanzapine (weight gain). Today, the chief complaint is lack of motivation to do chores around the house. The patient's sister notes that P.M. does not attend to activities of daily living unless reminded to do so and P.M. socially isolates most of the time. When asked about the reason for isolating, P.M. states that the patient just does not feel like making the effort, not from paranoia. P.M. denies feelings of depressed mood or suicidal thoughts. A mental status exam reveals a flattened affect, disheveled appearance, and normal speech and thought process. Comorbid medical conditions include diabetes and hypertension, which are currently well-controlled. BMI is 32.5 kg/m^2, most recent HbA1c is 6.8%, and blood pressure is 127/76 mmHg.

Nonpharmacologic treatments, such as cognitive behavioral therapy (CBT), social skills training, cognitive remediation therapy, and physical exercise have some evidence for improving negative symptoms. CBT is perhaps the most widely studied psychological intervention in schizophrenia and may be particularly beneficial in reducing apathy and improving motivation.[6] The European Psychiatric Association (EPA) advocates for the use of social skills training in patients with negative symptoms based on its review of published meta-analyses. The EPA also recommends considering cognitive remediation, particularly in those patients who also have cognitive impairment, and considering exercise as part of the integrated treatment plan.[58] The APA states that there is a moderate level of evidence supporting cognitive remediation in the treatment of negative symptoms and a low level of evidence to support social skills training.[10] Two recent meta-analyses demonstrate significant benefit of physical exercise in improving negative symptoms, particularly with aerobic exercise.[59,60] A summary of pertinent literature[5,50,51,59-74] regarding the management of negative symptoms of schizophrenia is available in Table 2. The same inclusion criteria were used as for Table 1.

Unfortunately, currently available antipsychotics are not widely effective in managing negative symptoms although SGAs have fewer EPS and greater antidepressant effects than FGAs and, therefore, may improve secondary negative symptoms.[75] The EPA recommends that patients treated with an FGA who experience negative symptoms should be switched to an SGA. Although it does not recommend a specific SGA, it does note that amisulpride and cariprazine have potential for managing negative symptoms and recommend clozapine in the context of treatment resistance.[58]

A 2018 systematic review and meta-analysis[67] in patients with predominant or prominent negative symptoms found that amisulpride (mean dose 50 to 300 mg/d) was the only antipsychotic superior to placebo; however, its benefits were mainly attributable to its antidepressant effects. Amisulpride is not currently available in an oral formulation in the United States although it is approved in intravenous form for postoperative nausea and vomiting, and a methylated oral formulation is currently in development.[76]

It should be noted that, in a study of cariprazine versus risperidone for negative symptoms, the authors controlled for potential secondary sources of negative symptoms (positive symptoms, depression, and EPS), whereas many other antipsychotic trials did not.[67,69] Due to the superiority of cariprazine in this study (least squares mean difference versus risperidone in PANSS factor score for negative symptoms = –1.46, 95% CI = –2.39, –0.53; $P = .0022$) and a lack of well-controlled studies with other SGAs, some experts call for use of cariprazine as a first line treatment of negative symptoms.[77] Cariprazine may be preferable in patients with prominent or predominant negative symptoms and well-controlled positive symptoms. It should ideally be titrated to a dose of at least 4.5 mg/d to target negative symptoms as higher doses (4.5 to 6 mg/d) are associated with greater benefit for negative symptoms.[68] Patients should be monitored for akathisia, a known dose-dependent adverse effect of cariprazine.

A 2019 meta-analysis[66] found that 18 out of 21 antipsychotics studied improved negative symptoms with clozapine having the largest effect size. This study, however, excluded patients with prominent negative symptoms. Clozapine may primarily exert its effect on negative symptoms through its prominent effect on positive symptoms, resulting in an improvement in secondary negative symptoms. There is very little evidence, however, to suggest that clozapine is superior to other antipsychotic medications in treating persistent negative symptoms in patients with only limited positive symptoms.[58]

Additional medications that demonstrate modest benefits in treating negative symptoms when used adjunctively with antipsychotics in clinical trials include modafinil/armodafinil, memantine, minocycline, and NAC; however, potential issues in trial design, such as a short duration, small sample size, and variable definitions for negative symptoms, make these results difficult to apply to clinical practice (see Table 2).[58,75] Pimavanserin, a selective 5-HT$_{2A}$ receptor inverse agonist and antagonist that is currently FDA approved for the treatment of psychosis in patients with Parkinson disease, has recently been studied[5] as an adjunct to antipsychotics for the treatment of negative symptoms in schizophrenia. In a 26-week, phase 2 study of pimavanserin 10 to 34 mg/d in patients with predominant negative symptoms, the mean change in the 16-item Negative

TABLE 2: Clinical studies of interventions for negative symptoms

Nonpharmacologic Interventions			
Intervention	**Studies**	**Results**	**Conclusions**
Psychological and psychosocial interventions	Systematic review and meta-analysis[61] of 95 RCTs (n = NR) published up until Oct 19, 2015	• Compared with treatment as usual, CBT (SMD = –0.34, 95% CI = –0.55, –0.12), skills-based training (SMD = –0.44, 95% CI = –0.77, –0.10), exercise (SMD = –0.36, 95% CI = –0.71, –0.01), and music treatments (SMD = –0.58, 95% CI = –0.82, –0.33) had significant benefit • Interventions lasting longer than 45 cumulative min/wk were significantly effective (pooled SMD = –0.341, 95% CI = –0.558, –0.125), whereas those offered less than 45 min/wk were not (pooled SMD = –0.024, 95% CI = –0.373, 0.324)	• Nonpharmacologic treatments such as CBT, exercise, music therapy, and skills-based training yielded moderate benefit in negative symptoms • These interventions should be offered for more than 45 min/wk
Cognitive remediation therapy (CRT)	Pairwise and network meta-analysis[62] of 45 RCTs (n = 2511) published between 1991 and 2015	• CRT was superior to TAU/active control (Hedge g = 0.35, 95% CI = 0.25, 0.44) • Studies integrating CRT with rehabilitation showed the greatest effect	• CRT has moderate benefit in treating negative symptoms • CRT should preferably be combined with psychiatric rehabilitation
Physical exercise	• Meta-analysis[59] of 22 RCTs (n = 1249) published up until Apr 26, 2018 • Meta-analysis[60] of 17 RCTs (n = 954) published between 2010 and 2018	• Physical exercise overall effect sizes = 0.24-0.43 • Mind-body exercise effect size in one meta-analysis = 0.46 (95% CI = 0.13, 0.79) • Aerobic exercise effect sizes = 0.31-0.34	• Exercise (mind-body and aerobic) may produce a small to medium benefit in negative symptoms
rTMS and tDCS	• Meta-analysis[63] of 22 RCTs of rTMS (n = 825) and 5 studies of tDCS (n = 134) published up until Dec 2017 • Meta-analysis[64] of 24 RCTs of rTMS (n = 1086) and 7 studies of tDCS (n = 169) published up until Apr 30, 2017	• rTMS vs sham treatment effect size = 0.19-0.64 • One secondary analysis suggests that rTMS may be more effective in younger patients (younger than the mean age of 39.1 y, effect size = 0.46) than older patients (older than 39.1 y, effect size = 0.26) • Another secondary analysis found a greater effect of rTMS in patients with fewer than 13 y of illness (effect size = 0.56) vs longer duration of illness (effect size = 0.29) • tDCS not significantly superior to sham stimulation in one analysis, but superior in the other (Hedge g = 0.5, 95% CI = 0.02, 0.97)	• rTMS may have a small-medium effect on negative symptoms with potentially greater effects in younger patients with a shorter duration of illness • tDCS is not consistently effective
Social skills training	Meta-analysis[65] of 27 RCTs (n = 1437; publication dates not specified)	• Social skills training was superior to all comparators pooled (Hedge g = 0.191, 95% CI = 0.043, 0.33), treatment as usual (Hedge g = 0.311, 95% CI = 0.078, 0.544), and active controls (Hedge g = 0.196, 95% CI = 0.01, 0.383)	• Social skills training produces a small benefit in negative symptoms

Symptom Assessment was significantly better than placebo. The authors[5] concluded that further research is warranted, and phase 3 trials[78] are currently underway. Given the relatively strong study design, pimavanserin may be an appropriate choice for adjunctive treatment in patients with well-controlled positive symptoms but persistent negative symptoms.

The EPA recommends considering adjunctive use of an antidepressant if negative symptoms do not improve after antipsychotic optimization. It does not recommend a specific class or medication but notes that SSRIs are the most studied.[58] The APA guideline also states that augmentation of antipsychotics with antidepressants may be helpful in patients with negative symptoms.[10] Meta-

TABLE 2: Clinical studies of interventions for negative symptoms (continued)

Pharmacologic Interventions			
Intervention	**Studies**	**Results**	**Conclusions**
Antipsychotics	• Network meta-analysis[66] of 132 RCTs (n = 32 015) published up until Jan 9, 2019 • Systematic review and meta-analysis[67] of 21 RCTs in patients with predominant or prominent negative symptoms (n = 3451) published up until Dec 12, 2017	• 18 out of 21 antipsychotics significantly improved negative symptoms in network meta-analysis (SMD = –0.22 to –0.62) • Overall, clozapine had the largest effect size (SMD = –0.62, 95% CI = –0.84, –0.39) followed by zotepine (SMD = –0.54, 95% CI = –0.77, –0.31) and amisulpride (SMD = –0.5, 95% CI = –0.64, –0.37) • Amisulpride (MDD 50 to 300 mg) was superior to placebo (SMD = 0.47, 95% CI = 0.23, 0.71) in patients with predominant or prominent negative symptoms • Meta-analysis of other antipsychotics in predominant or prominent negative symptoms were not possible due to the small number of trials, but single studies found cariprazine (MDD 4.2 mg), olanzapine (MDD 5 to 20 mg), and quetiapine (MDD 455.8 to 637.2 mg) superior to risperidone (MDD 3.51 to 4.9 mg; SMD = –0.29, –0.3, and –1.34, respectively) and olanzapine (MDD 5 to 20 mg) superior to haloperidol (MDD 4.2 to 24.1 mg; SMD = 0.75, 95% CI = 0.06, 1.44)	• Antipsychotics produce a small-to-medium effect on negative symptoms • Whereas clozapine may have the most significant benefit overall, this effect may be related mostly to its effect on positive symptoms • In patients with prominent/predominant negative symptoms, amisulpride appears to be the most promising; however, oral formulation not available in the United States
Cariprazine	• Post hoc analysis[68] of patients with moderate-severe negative symptoms from 2 double-blind, placebo-controlled RCTs (n = 317) • 26-wk double-blind, risperidone-controlled RCT in stable patients with predominant negative symptoms[69] (n = 456)	• Compared to placebo, there was a significant reduction in negative symptoms in the cariprazine 1.5 to 3 mg/d group (Cohen d = 0.41), cariprazine 4.5 to 6 mg/d group (Cohen d = 0.71), and risperidone 4 mg/d comparator group (Cohen d = 0.57) vs placebo • After adjusting for changes in positive symptoms, negative symptom benefit for cariprazine remained statistically significant, but risperidone did not • Cariprazine 4.5 mg/d was also significantly superior to aripiprazole (Cohen d = 0.5) • Cariprazine (MDD 4.2 mg) was found superior to risperidone (MDD 3.8 mg) in head-to-head study (LSM change in PANSS-FSNS = –1.46, 95% CI = –2.39, –0.53, P = .0022, Hedge g = 0.31) with similar rates of adverse effects	• Cariprazine may have a dose-dependent benefit in managing negative symptoms, particularly in patients with moderate-severe symptoms • Cariprazine appears to be superior to risperidone in treating predominant negative symptoms
Pimavanserin	26-wk double-blind, placebo-controlled RCT in patients with predominant negative symptoms[5] (adjunctive to ongoing antipsychotic)	• Pimavanserin 10 to 34 mg/d had significant reduction in negative symptoms as measured by the NSA-16 (–10.4 vs –8.5, P = .043; effect size 0.211) • Patients treated with a higher dose (34 mg) had greater effect (effect size = 0.34) • The most common adverse effects were headache (6% vs 5% with placebo) and somnolence (5% vs 5%)	• Pimavanserin had a small but significant and possibly dose-dependent effect on negative symptoms • Results should be confirmed in future phase 3 trials • Pimavanserin appears to be well-tolerated in this patient population

TABLE 2: Clinical studies of interventions for negative symptoms (continued)

Adjunctive Pharmacologic Interventions			
Intervention	**Studies**	**Results**	**Conclusions**
Antidepressants	Meta-analysis[70] of 42 placebo-controlled RCTs (n = 1934) published up until Oct 10, 2017	• Antidepressants overall performed significantly better than placebo (SMD = –0.25, 95% CI = –0.44, –0.06) • Antidepressants were effective adjunctive to FGAs (SMD = –0.42, 95% CI = –0.77, –0.07) but not SGAs (SMD = –0.23, 95% CI = –0.54, 0.08) • SSRIs (SMD = –0.26, 95% CI = –0.49, –0.03) and SNRIs (SMD = –1.3, 95% CI = –2.0, –0.6) were effective, but other antidepressant classes were not • Antidepressants were not associated with more adverse effects than placebo	• Antidepressants produce a small benefit in managing negative symptoms • The benefit of adding an antidepressant may be larger in patients treated with FGAs • SSRIs and SNRIs have the most evidence supporting use, whereas other antidepressants need further study
Escitalopram	8-wk double-blind, placebo-controlled RCT[71] (n = 54)	• Escitalopram (titrated up to 20 mg/d) group had significantly greater reduction in negative symptom subscale of PANSS vs placebo (–4.3 vs –1.7, $P < .001$) • Escitalopram group had greater reductions in IL-6 levels ($P < .001$) • Side effects included emesis (2 patients in placebo group) and dry mouth (1 in escitalopram group and 1 in placebo group)	• This study adds to the abovementioned evidence base for SSRIs in managing negative symptoms • Antidepressant benefit may be related to anti-inflammatory effects
Anti-inflammatory medications	Meta-analysis[72] of 56 double-blind, placebo-controlled RCTs (n = NR) published up until Aug 9, 2018	• Interventions that had a significant effect on negative symptoms and included at least 2 studies were estrogen 0.05 to 2 mg/d, raloxifene 60 to 120 mg/d (Hedge g = 0.45, $P = .006$), minocycline 100 to 300 mg/d (Hedge g = 0.5, $P = .003$), and NAC 600 to 3600 mg/d (Hedge g = 0.75, $P = .009$) • Most of the estrogen/raloxifene studies (9 out of 11) included only women	• Minocycline and NAC may have a moderate-large effect on negative symptoms • Estrogen-based treatments may be effective in females with further study needed in males
Memantine	• Systematic review and meta-analysis[50] of 8 double-blind, placebo-controlled RCTs (n = 448) published up until Mar 14, 2017 • Meta-analysis[51] of 8 RCTs (n = 452) published up until Dec 15, 2016	• Memantine 20 mg/d was superior to placebo in treating negative symptoms SMD = –0.63 to –0.96 • In 1 meta-analysis, younger age was associated with greater improvement ($P = .021$) • No significant difference between groups in adverse effects	• Memantine has a moderate-large effect on negative symptoms • Younger patients may have greater benefit from memantine
Pro-dopaminergic agents	Meta-analysis[73] of 10 RCTs (n = 450) published up until Jan 18, 2018	• Medications studied included modafinil (MDD = 183.5 mg; n = 176), armodafinil (MDD = 175 mg; n = 200), pramipexole (MDD = 4.25 mg; n = 24), and levodopa (MDD = 265 mg; n = 50) • Overall, pro-dopaminergic medications did not significantly reduce negative symptoms • An analysis of the 4 studies that required a minimum threshold for negative symptom severity showed a significant effect of modafinil/armodafinil versus placebo (SMD = –0.27, 95% CI = –0.52, –0.02) • No significant increase in positive symptoms	• Modafinil/armodafinil may provide a small benefit in patients with moderate-severe negative symptoms without exacerbating positive symptoms

TABLE 2: Clinical studies of interventions for negative symptoms (continued)

Adjunctive Pharmacologic Interventions			
Intervention	**Studies**	**Results**	**Conclusions**
Vitamin and mineral supplementation	Systematic review and meta-analysis[74] of 18 RCTs (n = 832) published up until July 2016	• Zinc 150 mg/d significantly reduced negative symptoms over 6 wks in 1 study (n = 29, *P* = .02) • No significant effect on negative symptoms found for B vitamins, vitamin C, inositol, or chromium	• Vitamin and mineral supplements do not appear to be effective in treating negative symptoms • Zinc had promising results in one small study that requires replication

CBT = cognitive behavioral therapy; CI = confidence interval; LSM = least squares mean; MDD = mean daily dose; NR = not reported; PANSS-FSNS = PANSS-factor score for negative symptoms; SMD = standardized mean difference; TAU = treatment as usual.

analyses have found small-to-medium effect sizes for antidepressants (Cohen d = −0.349; SMD = −0.3) with a larger effect in patients with predominant negative symptoms (SMD = −0.58).[79] A meta-analysis[70] published in 2018 found that SSRIs and SNRIs were statistically superior to placebo in the management of negative symptoms but only when used adjunctive to FGAs not SGAs. A subsequent study[71] of escitalopram titrated up to 20 mg/d showed significant improvement in negative symptoms when taken adjunctively to SGAs; however, the sample size was small. It may be preferable to use a less sedating and more activating SSRI, such as escitalopram or fluoxetine, over a sedating medication with greater anticholinergic burden, such as paroxetine.

Case 2 Discussion

P.M. appears to have relatively stable positive symptoms but is struggling with negative symptoms, such as avolition and social withdrawal. Social skills training should be recommended, if available, as recommended by the EPA guidance. Given the lack of other concrete recommendations, considering the following options and discussing them with the patient using a shared decision-making approach would be most appropriate. Switching iloperidone to cariprazine or clozapine could be considered; however, the patient has cardiometabolic disease and may not want to try clozapine given the patient's history of weight gain with olanzapine. Furthermore, the benefit of clozapine for negative symptoms seems to be mostly driven by its effect on positive symptoms. As this patient has had a history of adverse effects related to antipsychotics, only one true treatment failure, and positive symptoms are currently minimal, cariprazine may be the preferable choice. Alternately, adding an SSRI could be considered, particularly if the patient does not wish to change the antipsychotic. Given the risk of QTc prolongation with iloperidone, an SSRI with lower risk of QTc prolongation, such as sertraline or fluoxetine, would be preferable. If fluoxetine is selected, the dose of iloperidone would need to be reduced by half due to the CYP2D6-mediated interaction. Regardless, recommending physical exercise and CBT would be appropriate to help improve motivation. Pimavanserin may be considered, but its evidence is preliminary, and as a branded, off-label medication, the expense would be considerable. It also has a warning for QTc prolongation.

Case 3: Medications That May Worsen Negative and Cognitive Symptoms

J.N. is a 57-year-old patient with schizophrenia and generalized anxiety disorder who is currently managed on ziprasidone 60 mg twice daily and benztropine 1 mg twice daily. Other medications include levothyroxine 88 mcg daily, amlodipine 10 mg daily, paroxetine 40 mg daily, and lorazepam 1 mg 3 times daily. J.N.'s outpatient psychiatrist recently retired, and J.N. is transferring to your outpatient mental health clinic. The patient's pharmacy confirms that the patient has been on the same medications and doses for the past 3 years and has an allergy to haloperidol listed in the patient's profile with a reaction of "lockjaw" reported. The patient does not recall experiencing this side effect with any other medications in the past. J.N. currently denies any symptoms of psychosis but does endorse forgetfulness and difficulty remembering what the patient needs to purchase at the grocery store. Medical conditions and generalized anxiety disorder are stable, and a recently performed Abnormal Involuntary Movement Scale indicated no evidence of tardive dyskinesia.

Many studies of interventions for cognitive and negative symptoms do not differentiate between symptoms that are primary (part of the disease itself) or secondary to other causes, including medication side effects.[2,58] Differentiating between negative symptoms, such as affective flattening and alogia, and antipsychotic-induced parkinsonism may be particularly difficult. The EPA guideline on assessment of negative symptoms recommends paying particular attention

to changes in the time course of symptoms related to medication changes. The patient should also be assessed for the presence of other EPS symptoms, such as tremor or rigidity.[2] The EPA recommends a switch to an antipsychotic with lower risk for EPS or sedative side effects if these adverse effects are identified as a potential cause of negative symptoms.[58]

Antipsychotic-induced parkinsonism may also have adverse effects on cognition even in the absence of noticeable motor symptoms. When managing antipsychotic-induced parkinsonism in the context of CIAS, amantadine may be preferable due to its lack of anticholinergic properties; however, its use would need to be weighed against the risk of adverse effects, including worsening psychosis.[10] Sedation from antipsychotics may also reduce cognitive acuity. Antipsychotic medications with high levels of antihistaminergic activity and sedation, such as quetiapine, can lead to significant cognitive impairment.[80] The APA recommends lowering the daily dose of the antipsychotic, consolidating the dose into 1 evening dose, or changing to a less sedating agent (eg, aripiprazole, paliperidone) if sedation occurs with antipsychotic treatment.[10]

Benzodiazepines, although useful in the management of agitation or akathisia, can also have significant sedating effects and contribute to cognitive dysfunction.[10,81] Reduction or discontinuation of benzodiazepines in patients with schizophrenia is associated with improvements in the BACS total score and verbal and working memory as well as increased motivation/energy as measured by a quality-of-life scale in 1 study[82] and significant improvements in all cognitive domains of the BACS except for motor speed in another study.[83]

Anticholinergic medication burden is a significant contributor to cognitive dysfunction in schizophrenia and may even lessen the response to cognitive remediation.[84] Several studies have recently linked anticholinergic burden to impaired cognition and functional outcomes.[80] Assessing and limiting anticholinergic burden may help improve CIAS. The Anticholinergic Drug Scale (ADS) is one validated tool that can be used to quantify anticholinergic burden in a patient's drug regimen. In 1 large study of patients with psychotic disorders, patients with schizophrenia and an ADS score of $\geq$4 had lower composite scores on the BACS compared with patients with lower ADS scores. Verbal memory was the most significantly affected variable.[85] Another study found that patients with ADS scores $\geq$3 had poorer cognitive function as measured by the MCCB as well as lower daily living function as measured by the University of California San Diego Performance-based Skills Assessment.[86]

The Anticholinergic Cognitive Burden (ACB) scale is another validated scale with established utility in predicting dementia risk in healthy subjects. A large study of patients with schizophrenia or schizoaffective disorder recently found that a higher ACB score was significantly associated with worse cognitive performance as measured by the Penn Computerized Neurocognitive Battery.[87] Khan and colleagues also assessed the effect of anticholinergic burden on cognition in patients with schizophrenia or schizoaffective disorder using the ACB scale.[88] In their sample of 223 outpatients, 63.7% of participants had an ACB score of 3 or greater, a threshold that has previously been associated with a risk of cognitive impairment in older adults.[88,89] Patients with higher ACB scores who were 55 years or older had worse cognition as measured by the MCCB, including global cognition (P = .012), attention/vigilance (P = .008), and speed of processing (P = .019). There was no statistically significant relationship between ACB and cognitive scores in younger patients; however, higher ACB was associated with lower functional capacity even after controlling for age.[88]

Many patients end up on anticholinergic medications long term for prophylaxis of EPS; however, the APA states that the long-term benefits are unclear, and the potential harms may outweigh the risk given the potential effects on cognition as well as other burdensome side effects, such as dry mouth, urinary retention, and constipation. The APA has called for future research to determine the optimal duration of treatments for EPS.[10] Lupu and colleagues recently reported results of a quality improvement initiative aimed at reducing chronic anticholinergic medication (ACM) use in patients with severe mental illness. They provided education to psychiatrists combined with clinical pharmacy support for deprescribing and targeted patients with no current signs of EPS taking ACM for at least 6 months. In this sample, more than 75% of patients were able to successfully reduce or discontinue ACM over 1 to 6 months. Perhaps most importantly, this reduction in ACM was associated with significant improvements in memory impairment, anticholinergic side effects, and quality of life. Only 10% of patients needed to be restarted on ACM for reemergent EPS.[90]

Case 3 Discussion

J.N. has been taking anticholinergic medication for at least 3 years, per pharmacy records. Although the patient has a history of dystonia related to haloperidol, it is unclear if J.M. had EPS with other medications. It would be reasonable to attempt to taper the benztropine at this time and monitor closely for the reemergence of EPS. Clinical studies utilize tapers of 1- to 6-month durations.[90,91] A reasonable strategy would be to taper the benztropine to a total daily dose of 75% of the original dose (eg, benztropine 0.5 mg daily in the morning and 1 mg daily at bedtime) for several weeks, followed by a reduction to 50% of the original dose for several weeks (benztropine 0.5 mg twice daily), then 25% of

the original dose (eg, benztropine 0.5 mg daily at bedtime) for several weeks, followed by discontinuation with a follow-up phone call or visit scheduled after each dose reduction to monitor for potential emergence of EPS and potential improvement in cognitive symptoms. Additional medications that may be causing adverse cognitive effects include paroxetine and lorazepam. Given that this patient's anxiety appears to have been relatively stable, a discussion should be had about gradually tapering off the lorazepam. In clinical studies of patients with schizophrenia who were chronically using benzodiazepines, a taper of 10% to 50% of the daily dose every 2 to 4 weeks over a 24-week period has been successfully completed on an outpatient basis.[82,83] If the patient is able to successfully discontinue lorazepam but still experiences cognitive dysfunction, switching paroxetine to an alternative SSRI with less anticholinergic burden (eg, fluoxetine, escitalopram) should be considered.

Conclusion

Cognitive and negative symptoms associated with schizophrenia contribute significantly to the burden of illness experienced by patients and caregivers; however, conventional antipsychotic treatments are often minimally effective in managing these symptoms. Nonpharmacologic treatments, such as cognitive remediation, are recommended by clinical practice guidelines but may not be readily available. Exercise may also be beneficial in improving cognitive and negative symptoms with the added benefit of reducing cardiometabolic risk. Although most of the literature supporting the use of pharmacologic treatments is lacking in rigor with small sample sizes and heterogeneity between studies, psychiatric pharmacists can aid in selecting potentially beneficial treatments and weighing them against potential risks in individual patients. Furthermore, pharmacists can play a key role in identifying potentially inappropriate medications that may be causing secondary negative symptoms or worsened cognition and facilitating careful deprescribing and/or substitution of these agents.

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