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RESEARCH ARTICLE

Less is more: Deprescribing anticholinergic medications in persons with severe mental illness

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BACKGROUND: Long-term prescribing of anticholinergic medications (ACM) for antipsychotic-associated extrapyramidal symptoms (EPS) is not recommended, yet is widely prevalent. Adverse effects of ACM include memory impairment, dry mouth, constipation, blurred vision, urinary retention, and tachycardia, which can seriously impact quality of life. This quality improvement deprescription project sought to reduce chronic ACM use in patients with serious mental illness (SMI).

METHODS: Education directed at psychiatrists combined with clinical pharmacy support for deprescription was used to target clinically stable patients diagnosed with schizophrenia, schizoaffective disorder, or bipolar disorder with no EPS and ACM prescriptions of ≥6 months. Scales were used to assess anticholinergic adverse effects, memory impairment, and quality of life. ACMs were tapered and discontinued over 1 to 6 months.

RESULTS: More than 75% of targeted patients successfully tapered or discontinued ACM, which coincided with significant improvements in anticholinergic adverse effects, memory impairment, and quality of life. Approximately 10% of patients were restarted on ACM for re-emergent EPS.

CONCLUSIONS: For most clinically stable patients with SMI without EPS, our findings suggest that gradual deprescription of chronic ACM is clinically appropriate, well tolerated, and improves quality of life. A randomized trial could provide more definitive answers.

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INTRODUCTION

Antipsychotic-induced extrapyramidal symptoms (EPS) can present as parkinsonian features, akathisia, and/or dystonic movements.[1-3] Although commonly associated with first-generation, high-potency, dopamine-2 (D2) receptor antagonists, EPS also are known to occur with some newer antipsychotic medications.[4] EPS are thought to stem from antagonism of D2 receptors in the nigrostriatal pathway, leading to an imbalance of inhibitory dopaminergic and excitatory cholinergic neurotransmission.[5] Anticholinergic medications (ACM) that act on muscarinic receptors, such as benztropine and trihexyphenidyl, are FDA-approved for parkinsonism and mitigate EPS by restoring this neurotransmitter imbalance.[6] ACM are associated with a constellation of adverse effects, including dry mouth, constipation, blurred vision, impaired memory, urinary retention, and tachycardia.[6-9] These systemic adverse effects, as well as ACM's contribution to the prevalent medication burden of patients with serious mental illness (SMI), can significantly impact patients' quality of life, lead to treatment nonadherence, and otherwise undo clinical gains.[10]

There is considerable variation in ACM use among patients with SMI across countries and regions. A recent large survey (>3,500 patients) of persons with schizophrenia in several Asian countries reported that nearly 46% of patients received ACM.[11] A study of stable community-dwelling outpatients with schizophrenia (N = 674) in France reported that 20% of participants were prescribed an ACM.[12] Among 300 patients prescribed first-generation antipsychotics (FGAs) and attending ambulatory clinics at Ethiopia's only specialty psychiatric hospital, more than one-half (54.3%) received trihexyphenidyl, and 24.3% of patients described anticholinergic adverse effects.[13] In Denmark, the use of ACM among patients with schizophrenia decreased from 11.7% in 1996 to 5.7% in 2012, with regional differences noted across the country.[14] In the United States, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study assessed the clinical effectiveness of second-generation antipsychotics (SGAs) (olanzapine, quetiapine, risperidone, and ziprasidone) and 1 FGA (perphenazine) in 1,493 patients with chronic schizophrenia recruited at 57 centers.[15] The rate of EPS as measured by the Simpson Angus Scale for EPS[16] was 4% to 8% across the SGAs, but also was low for perphenazine (6%).[15] The rates of ACM use were low in the CATIE study, and varied significantly among the 5 antipsychotic agents: perphenazine, 10%; risperidone, 9%; ziprasidone, 8%; olanzapine, 8%; and quetiapine, 3%.[15] However, in the Bipolar–Schizophrenia Network on Intermediate Phenotypes study, also conducted across several sites in the United States, ACM use was nearly 19% among 397 persons with schizophrenia, most of whom (78.6%) received a SGA.[17]

The World Health Organization (WHO)[18] discourages prophylactic and long-term ACM treatment for antipsychotic-induced EPS. However, in clinical practice, ACM often are prescribed preventatively and—even in the absence of EPS—continued for extended periods of time.[12,19] Long-term use of these medications has been linked to poor clinical outcomes, including impaired cognitive functioning, blurred vision, dry mouth, constipation, urinary retention, tachycardia, worsening positive symptoms of psychosis, tardive dyskinesia, and greater medication burden, any of which can lead to antipsychotic nonadherence.[20,21] This report describes a quality improvement (QI) project to deprescribe ACM in clinically stable outpatients with SMI without EPS. The primary objective of the project was to reduce ACM-associated adverse effects and improve patient quality of life. A secondary objective was to create a clinical pathway decision support tool, based on our results and supplemented by data from our previous pilot project,[22] to assist prescribers in clinically appropriate deprescribing of ACM.

METHODS

This QI initiative was approved as an extension of an earlier pilot project[22] by the University of Pittsburgh Medical Center (UPMC) Quality Improvement Review Committee, and therefore separate institutional review board approval was not required. The goal of the pilot project was to reduce ACM burden in a small group of patients with SMI who received care at the Comprehensive Recovery Service Clinic of UPMC Western Psychiatric Hospital. In this expanded project, we targeted all patients prescribed benztropine or trihexyphenidyl through our internal pharmacy (Forbes Pharmacy) for potential QI inclusion.

Setting and patients

The Comprehensive Recovery Service clinic treats patients with SMI, including those with schizophrenia, schizoaffective disorder, and bipolar disorder as described in DSM-5. Patients have access to several health care services within

the same building, including psychiatric and psychotherapy services, psychiatric rehabilitation, clinical laboratory services, and medication dispensing through the co-located Forbes Pharmacy, which also provides clinical pharmacy services. Clinical pharmacists provide medication and disease state education and make recommendations to ensure safe and effective medication use.

Intervention

To provide knowledge about the benefits of deprescribing ACM in stable outpatients with SMI, the successful methods and results of the pilot QI project[22] were disseminated to attending and resident psychiatrists (n = 14) using a small-group educational format (ie, problem-based learning) with continuing medical education certification. After this educational session, a medication dispensing report was generated to identify all patients of Forbes Pharmacy who were co-prescribed ≥1 antipsychotic medication and benztropine or trihexyphenidyl for ≥6 months. After the attending psychiatrists and psychiatric residents had attended the educational session, they received personalized emails with an introduction to, and results of, the pilot project,[22] as well as the name of each patient on their caseload identified by the report. Psychiatrists were requested to refer patients from the list who they thought were clinically stable and might benefit from a pharmacy consultation for possible taper or discontinuation of ACM. During the initial consultation, the clinical pharmacist conducted a comprehensive medication review, including medication reconciliation, to identify all possible ACM and to assess anticholinergic adverse effects and their impact on quality of life. Recommendations for potential medication changes were reviewed with the patients and referring psychiatrists. When clinically appropriate, benztropine or trihexyphenidyl was tapered and/or discontinued by the psychiatrists over 1 to 6 months, at their clinical discretion, with follow-up assessments with clinical pharmacists in the interim. Patients who had a medication change were monitored for re-emergent EPS, and if this occurred, ACM were restarted; in a few cases, EPS resolved at lower dosages. The status of each patient's ACM use was updated 6 months after their last visit with the clinical pharmacist, but no additional assessments were completed at that time.

Measures

Anticholinergic medication burden. The Anticholinergic Cognitive Burden (ACB) scale[23] is a widely used and validated scale[24] that categorizes the severity of potential anticholinergic adverse effects by providing a score for medications with anticholinergic properties. Medications with no anticholinergic activity are assigned a score of 0; those with laboratory evidence of antagonist activity at muscarinic receptors are scored as 1; those with evidence of clinical anticholinergic adverse effects from the literature, manufacturer's information, or expert opinion receive a score of 2; and those ACM with established and clinically relevant cognitive anticholinergic effects and the potential to cause delirium receive the highest score of 3. The scale's authors concluded that for each individual patient, a total score of ≥3 on the ACB was clinically significant, especially in terms of cognitive impairment in geriatric patients. In our project, the ACB was scored by the clinical pharmacist based on the patients' reconciled medication lists at the beginning and end of the intervention as an objective measure of ACM burden.

Anticholinergic adverse effects. Anticholinergic symptoms and their impact on quality of life were assessed using the Pittsburgh Anticholinergic Symptom Scale (PASS) developed by one of the authors (KNRC). Although the scale has not been validated psychometrically, it has been used in our clinics for several years, most recently in the pilot QI project.[22] Some items were modified from the original scale described in the pilot project to make it shorter and more patient-friendly. One item (dry skin) was omitted because it was a general complaint. The rating scale score was changed from a range of 1 to 10 (1 = never had symptoms, 10 = symptoms present every day) to a range of 0 to 6 (0 = no symptoms at all, 6 = symptoms all day and every day). This modification anchored the ACM adverse effects to the number of days during the last week that these adverse effects troubled participants. Utilizing the 0-to-6 range of scores for each item, patients self-rated the extent to which they experienced specific anticholinergic adverse effects during the past week: dry mouth, blurred vision, fast heartbeat, difficulty urinating, constipation, and confusion/memory problems (**FIGURE 1**). The total scores on the modified PASS scale (version 2.0) range from 0 to 36. Additionally, the single question from the earlier PASS version that assessed quality of life (QOL) was modified to 2 questions to more clearly capture the impact of ACM-associated adverse effects on patients' daily functioning. Each of the 2 QOL items scores also range from 0 to 6; therefore, the minimum total QOL score is 0 and the maximum score is 12. At referral and completion of the intervention, most patients completed the PASS and QOL

FIGURE 1

Pittsburgh Anticholinergic Symptom Scale – Patient Assessment Form (PASS Version 2.0)
How often do you have these symptoms?
Think about the past week. *Circle a number.*

	NOT AT ALL			HALF THE WEEK			EVERY DAY
							
Dry mouth	0	1	2	3	4	5	6
Blurred vision	0	1	2	3	4	5	6
Fast heartbeat	0	1	2	3	4	5	6
Difficulty urinating	0	1	2	3	4	5	6
Constipation	0	1	2	3	4	5	6
Confusion or memory problems	0	1	2	3	4	5	6
How intense (severe) have these side effects been?	None 0	Trivial 1	Mild 2	Moderate 3	Marked 4	Severe 5	Intolerable 6
How much have these side effects interfered with your day to day functioning?	None 0	Minimal 1	Mild 2	Moderate 3	Marked 4	Severe 5	Unable to function 6

questions on their own, with as-needed assistance from the clinical pharmacists. Patients completed the PASS version 2.0 in 5 to 8 minutes.

Memory. A brief screening tool used to assess geriatric patients, the Memory Impairment Screen (MIS),[25] was employed to measure possible memory impairment at baseline and after a final ACM change (dose reduction or discontinuation). For this test, patients were shown a piece of paper with 4 words to remember and asked to read them out loud. The patients were then told that each word belongs to a category and asked to indicate which word belongs to which stated category. Patients were allowed up to 5 attempts to correctly categorize each word. Once a patient identified all 4 words and categories correctly, the paper was removed from sight, and the patient was told that they would be asked to remember the words in a few minutes. The patient was then engaged in a different conversation or activity during that time, then asked to recall the 4 words in any order. Patients received 2 points when they recalled a word without the category cue; 1 point if they required the category cue before recalling the word; and 0 points if they were not able to recall any words at all. A total MIS score of 5 to 8 indicates no memory impairment, and a score ≤4 indicates memory impairment with a sensitivity of 0.80 and specificity of 0.96 for Alzheimer's and other dementias.[25] In our earlier QI project[22] the "5-word recall" test from the Montreal Cognitive Assessment[26] was used to assess cognitive impairment, but the MIS was chosen for this expanded project because it is a delayed free recall and cued recall test of memory impairment[25] that could target the memory concerns associated with ACM.

Statistical analyses

Descriptive statistics were used to enumerate the patients' demographic and clinical characteristics. Categorical variables were evaluated using contingency statistics that included the Chi-square or Fisher exact tests. Independent and paired *t* tests were used to examine differences between independent or paired data if assumptions for using parametric statistics were met. Alternatively, nonparametric tests—the rank sum/Mann-Whitney test and the Wilcoxon signed rank test—were used for independent group and paired data, respectively, for small data sets or if data were not normally distributed. Associations between continuous measures were examined using Pearson (*r*) or Spearman (ρ) correlations. All statistical tests were 2-sided and the nominal type 1 error (alpha) was set at 0.05. Only complete data sets were analyzed (ie, available data for both pre- and post-intervention) and no imputations for missing data were applied.

Development of a clinical decision support tool

This QI project and the earlier pilot[22] informed the development of a clinical decision tool to guide physicians and other prescribers in deprescribing ACM, namely benztropine, trihexyphenidyl, or similar ACM used for EPS (eg, biperiden, procyclidine).

RESULTS

TABLE 1 describes the demographic, psychiatric diagnosis, and medication characteristics of the patients who participated in the QI project. The cohort consisted of 51 patients, 27 (53%) male and 24 (47%) female, with a mean age of 50.5 years; the youngest participant was a 22-year-old male, and the oldest was a 71-year-old female. Thirty-three patients identified as African American (65%), 15 as white (29%), and 3 as Asian (6%). Collectively, the 51 participants were under the care of 14 psychiatrists (including residents). Forty-three patients (84%) had a diagnosis of schizophrenia, 7 patients (14%) had schizoaffective disorder, and one patient had bipolar disorder. Forty-six patients (90%) were receiving benztropine; the remaining 5 (10%) were prescribed trihexyphenidyl. The cohort received an average of 8 medications (low: 2; high: 25). Most patients were prescribed 1 antipsychotic medication (n = 34; 65%), but 17 patients received 2 antipsychotic medications. Forty-one patients (80%) received ≥1 SGA. The most commonly prescribed SGA was clozapine (n = 18; 35%) followed by risperidone (n = 10; 20%). Of the 18 patients receiving clozapine, 12 were on a concomitant high-potency D2-blocking oral or long-acting injectable antipsychotic medication (ie, haloperidol, risperidone). Twenty-two patients (43%) were taking an FGA. The most commonly prescribed FGA was haloperidol (n = 9; 18%) followed by fluphenazine (n = 8; 16%). Twenty-two patients (43%) were prescribed a long-acting antipsychotic injection (LAI).

Overall, 38 of 51 patients (75%) stopped or reduced their ACM over 1 to 6 months. Four of the 38 patients (10%) had to restart their ACM 4 to 6 months after their last visit with the clinical pharmacist because of re-emergent EPS. Demographic and medication variables that

TABLE 1
Demographic, diagnosis, and illness characteristics of patients (N = 51)

Demographic/characteristic	Value
Sex	
Male	27 (53%)
Female	24 (47%)
Age (in years)	
Mean ± SD	50.5 (± 12.45)
Range	22 to 71
Race	
African-American	33 (65%)
White	15 (29%)
Asian	3 (6%)
Psychiatric diagnosis	
Schizophrenia	43 (84%)
Schizoaffective disorder	7 (14%)
Bipolar disorder	1 (2%)
Anticholinergic medication	
Benztropine	46 (90%)
Trihexyphenidyl	5 (10%)
Total number of medications	
Mean	8
Range	2 to 25
Antipsychotic medications[a]	
First-generation	22 (43%)
Second-generation	41 (80%)
>1 Antipsychotic	17 (33%)
Long-acting antipsychotic	22 (43%)

[a]Numbers and percentages add up to more than n = 51 or 100% because some patients are enumerated more than once in the >1 antipsychotic and long-acting antipsychotic rows.

could impact the likelihood of ACM reduction or discontinuation were analyzed for the cohort (n = 51). Age, sex, or race did not have a significant impact on ACM changes. Twenty-nine patients (57%) were receiving SGAs only, 10 patients (20%) were taking FGAs only, and 12 patients (23%) were receiving concomitant FGA and SGA prescriptions. Of the patients taking an SGA only or an SGA plus an FGA, 83% were able to discontinue or decrease the dosage of ACM, whereas significantly fewer patients (50%) on an FGA only were able to reduce or stop ACM (Fisher exact test, $P = .04$). Furthermore, the cohort of 22 patients taking LAIs had a significantly lower success rate of ACM discontinuation or dosage reduction compared with those taking oral medications (90% vs 59%; Fisher exact test, $P = .02$).

Twelve (24%) of the 51 patients identified for inclusion in the project were able to work with their psychiatrists to taper or discontinue the ACM without the need for referral to the clinical pharmacist. Thirty-nine patients (76%) were referred to the clinical pharmacist for assessment of ACM taper or discontinuation. Of the 39 patients, 13 were deemed to be clinically inappropriate for a medication change, either because they had ongoing EPS (8 patients), were not clinically stable from a psychiatric standpoint (2 patients) or refused to consider a change even after receiving counseling and education from the clinical pharmacist and psychiatrist (3 patients). The following results are reported for the remaining 26 patients for whom assessments of anticholinergic burden (ACB), frequency and severity of anticholinergic symptoms (PASS), memory (MIS), and quality of life (QOL) were carried out before and after ACM dosage reduction or discontinuation.

The mean ACB score was 7.72 at referral, and 5.44 post-intervention ($P < .001$), a 30% improvement (**TABLE 2**). The PASS version 2.0 mean score dropped from 10.46 at referral to 4.96 post-intervention ($P < .001$), a 52.6% improvement (**FIGURE 2**). Pre-intervention, the mean PASS version 2.0–QOL summary score was 3.58, and decreased to 1.42 ($P < .001$) post-intervention, a 60% improvement. There was a significant and moderately strong positive correlation between the change in the 6 items of the PASS version 2.0 and the change in QOL scores (Pearson $r = 0.47$; $P = .016$). At baseline, the mean verbal memory recall score on the MIS was 5.58, which increased to a mean score of 6.42 after the intervention ($P = .002$). We separately analyzed patients who had a baseline MIS score ≥5 (ie, no memory impairment) vs those with an MIS score ≤4 (ie, memory impairment) (**TABLE 2**). Patients with memory impairment at baseline showed a highly significant improvement in their MIS scores when the ACM was tapered or discontinued, and the size of the treatment effect was large (Hedges $g = 1.35$; 95% confidence interval, 0.61 to 2.48). The unimpaired memory group also trended towards improved MIS scores after taper or discontinuation of ACM, but the results were not statistically significant. Changes in both the PASS version 2.0 6-item total scores and QOL total scores from pre- to post-intervention were significantly better in the memory impaired group (Wilcoxon signed rank test, $z = -2.006$; $P = .045$ and

TABLE 2
Changes in anticholinergic medication burden and patient-reported anticholinergic symptoms and memory domains before and after intervention[a] (N = 26)

Scale	Baseline	Post-intervention	*t* test, *P* value
Anticholinergic Cognitive Burden Scale Score (mean ± SD)	7.72 ± 3.2	5.44 ± 3.3	$t = 8.513$, $P < .001$
PASS Score[b] (mean ± SD)	10.46 ± 6.2	4.96 ± 3.7	$t = 6.357$, $P < .001$
PASS[b] QOL Score (mean ± SD)	3.58 ± 2.5	1.42 ± 1.6	$t = 5.744$, $P < .001$
MIS[c] (mean ± SD), n = 26	5.58 ± 1.8	6.42 ± 1.7	$t = 3.528$, $P = .002$
MIS[d] (mean ± SD), n = 7	3.29 ± 0.95	4.86 ± 1.07	$P = .015$[d]
MIS[e] (mean ± SD), n = 19	6.42 ± 1.07	7.00 ± 1.49	$P = .059$[e]

[a]Intervention consisted of dosage decreases or discontinuation of benztropine or trihexyphenidyl.
[b]Sum of 6 patient-reported anticholinergic symptoms on PASS version 2.0; excludes the 2 QOL items on PASS version 2.0, as these were evaluated separately.
[c]The Memory Impairment Screen (MIS)
[d]Participants with an MIS score of ≤4, ie, memory impaired, Wilcoxon signed rank test, $z = -2.428$, $P = .015$.
[e]Participants with an MIS score of ≥5, ie, no memory impairment, Wilcoxon signed rank test, $z = -1.888$, $P = .059$.

PASS version 2.0: Pittsburgh Anticholinergic Symptom Scale; QOL: quality of life; SD: standard deviation.

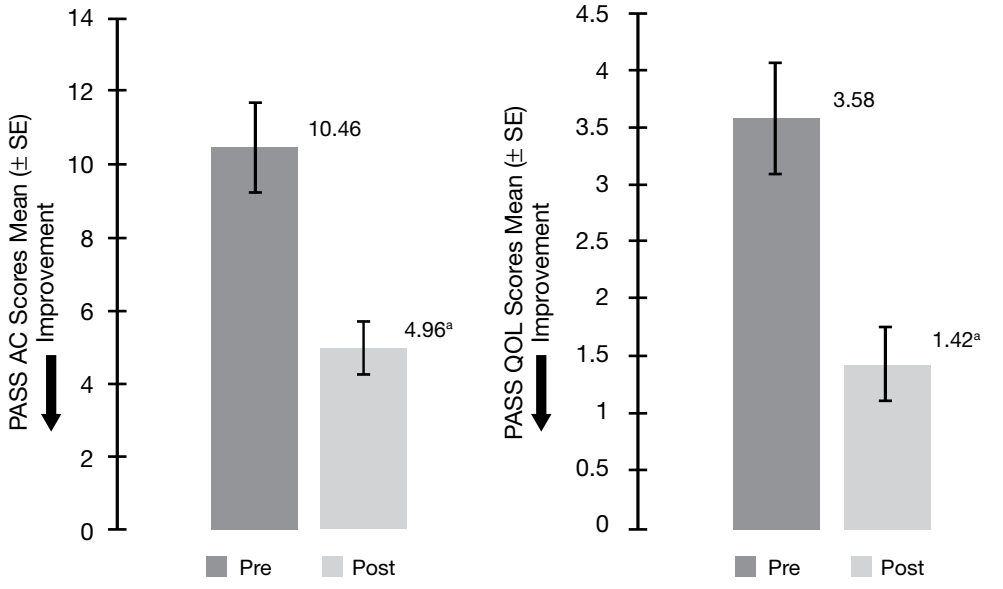
$z = -2.011$; $P = .044$) than in the memory unimpaired group. Race or sex were not associated with MIS change scores in the group as a whole, in the memory impaired group, or in the unimpaired group (data not shown). Age, however, was positively correlated (Spearman ρ) with MIS scores in the entire group ($\rho = 0.52$; $P = .007$), and trended similarly in the memory impaired group ($\rho = 0.73$; $P = .06$) and non-impaired group ($\rho = 0.44$; $P = .06$).

DISCUSSION

As implemented, this ACM deprescription QI project was successful. Three out of 4 patients with SMI who were clinically stable, without EPS, and receiving benztropine or trihexyphenidyl for an extended time were supported for gradual taper and discontinuation of their ACM by a health care team comprised of psychiatrists and clinical pharmacists. Moreover, and as expected, significant improvements in peripheral and central anticholinergic adverse effects occurred with the taper and discontinuation of ACM, and not surprisingly, these improvements coincided with a better quality of life. Importantly, patients with SMI and cognitive impairment at baseline showed a significant improvement in verbal recall memory after taper and discontinuation of ACM. A few patients (10%) continued to require long-term benztropine or trihexyphenidyl because they manifested re-emergent EPS after ACM taper and discontinuation. Six months after project completion, 34 of 38 patients (89%) who had changes to their ACM were maintained without ACM or were taking a lower dosage.

In our project, the treatment-related factors that were associated with an increased likelihood of ACM dose reduction or discontinuation were SGA therapy (alone or in combination with an FGA) and oral antipsychotic therapy vs LAI treatment. Eighty percent of patients in our project were receiving an SGA, a rate similar to that observed by Dong et al,[11] where >80% of patients were receiving an SGA,[11] and to Misdrahi et al,[12] where >90% of patients were receiving an SGA either alone or in combination with an FGA (20%).[12] Patients in the Misdrahi et al study[12] were further classified as having drug-induced parkinsonism (n = 89) vs not (n = 585) based on the Simpson-Angus scale for EPS.[16] Curiously, 15% of patients with SMI (n = 88) and without evidence of drug-induced parkinsonism were receiving ACM,[12] a group that could be targeted for ACM deprescription. In our project, clozapine was the most commonly prescribed SGA (n = 18; 35.3%). Nine (75%) of the 12 the patients receiving clozapine who were also receiving FGA or high-potency D2-blocking SGAs, such as risperidone, were able to stop their ACM. Clozapine has a low propensity to induce EPS because of its weak binding affinity for D2 (20% to 67%) and rapid dissociation,[27] a factor that likely contributes to the success of deprescription in our SGA cohort. ACM

FIGURE 2
Pittsburgh Anticholinergic Symptom Scale (PASS version 2.0) scores pre/post intervention to taper or stop anticholinergic medications



a*P* < .001.

AC: anticholinergic adverse effects; QOL: quality of life; SE: standard error.

sometimes are prescribed for treating hypersalivation in clozapine-treated patients.

After adjusting for confounders, Misdrahi et al[12] determined that drug-induced parkinsonism was associated with higher negative symptom burden, FGA prescription, and unsurprisingly, ACM prescription. In our project, 50% of patients receiving an FGA were able to discontinue or reduce the dosage of their ACM. A review of older studies of ACM discontinuation (eg, benztropine, trihexyphenidyl, biperiden, procyclidine, others) in patients with schizophrenia taking FGAs noted several methodological and analytic flaws,[28] but the rates of re-emergent EPS ranged from 7% to 70%, with the higher rates being noted with abrupt withdrawal of ACM. A crossover, within-subject study comparing 4 weeks each of ACM, placebo, or no ACM use showed no significant return of EPS in patients with schizophrenia who were maintained on an FGA and ACM for extended periods of time.[29] In a double-blind, placebo substitution trial that evaluated abrupt vs slow withdrawal (2 weeks) vs continuation of trihexyphenidyl in patients with psychosis maintained on an FGA for ≥6 months, 10 of 13 (77%) participants in the abrupt withdrawal group were reinstituted on trihexyphenidyl for re-emergent EPS, whereas only 3 of 11 (27%) in the taper group required a restart.[30] In a double-blind, placebo substitution study of stable patients with schizophrenia maintained on an FGA and trihexyphenidyl (11 years, mean dosage of 5 mg/d), gradual taper of trihexyphenidyl (1 mg every 2 weeks) resulted in 25 of 28 (89%) patients being discontinued successfully, and the remaining 3 patients achieved trihexyphenidyl dosage reductions with no worsening of mental state or return of EPS.[19] Based on the literature and our experience, ACM discontinuation is possible even in patients taking FGAs, and tapered discontinuation of ACM over weeks to months is advisable.

An additional finding in our project was that the cohort of patients prescribed an LAI either as monotherapy or in combination with an oral antipsychotic (n = 22; 41%) had a significantly lower rate of ACM discontinuation or dosage reduction. Some proposed advantages to using an LAI are increased medication adherence with potentially more stable blood levels, decreased pill burden, and regular follow-up with health care staff during injection appointments.[31] Improved adherence, especially with a potent D2-blocking LAI, could increase the likelihood of EPS because of more consistent blood levels

in these patients compared with poor adherence seen in those taking oral medications, although this was not assessed in our project. An LAI—especially an FGA—can cause breakthrough EPS shortly after administration, an important consideration for patients initiating or restarting therapy.[32] One limitation in interpreting this finding is that not all antipsychotics are formulated as both oral and depot injections. Moreover, we did not evaluate lifetime duration of antipsychotic treatment or perform statistical analysis based on FGA vs SGA LAI because of the small sample size. Nonetheless, nearly 60% of patients taking an LAI in our project were able to discontinue their ACM, highlighting the importance of reassessing the need for ACM in this group.

Assays of serum anticholinergic activity in geriatric patients and in persons with schizophrenia strongly and positively correlate higher anticholinergic serum levels with impaired learning and verbal memory, spatial working memory deficits, and other cognitive impairments.[8,33-39] In persons with schizophrenia, the illness itself is associated with considerable cognitive impairment.[40,41] Furthermore, ACM burden can seriously interfere with cognitive training and psychosocial rehabilitation for schizophrenia.[42,43] A few ACM studies have concentrated on cognitive improvements after ACM discontinuation. In 1 study, attention and concentration improved when ACM were tapered in clinically stable patients receiving an FGA.[44] In the modern SGA era, ACM deprescription has led to improvements in immediate and verbal working memory,[45] and improvements in ideational praxis and orientation in geriatric patients with schizophrenia (mean age: 66 years).[46] Ogino et al[47] deprescribed ACM over 2 to 4 weeks in patients with SMI receiving an SGA and recorded improvements in attention, processing speed, and global cognitive scores, including quality of life. Desmarais et al[21] noted modest improvements in motor and symbol-coding tasks on a standardized cognitive battery after ACM taper and discontinuation over 4 weeks (mean duration of ACM use: 6 years) in stable outpatients with schizophrenia. They did not see re-emergence of EPS in 18 of 20 outpatients (90% success), but 2 of 20 participants re-experienced akathisia. Our group noted improvements in 5-word short-term memory recall after ACM taper or discontinuation in stable outpatients with SMI.[22] The deprescription of ACM might mitigate cognitive impairments typically associated with ACM, a treatable and modifiable risk factor for neurocognitive impairment,[22,47-52] and therefore facilitate psychosocial rehabilitation in schizophrenia.

To our knowledge, this project might be the first to use the MIS[25] for both screening for ACM-induced memory impairment as well as assessing for changes with deprescription of ACM. The Buschke Selective Reminding Test,[53] a forerunner of the MIS, is known to be disrupted by ACM.[54] Refinements to the Buschke Selective Reminding Test were developed, included the Free and Cued Selective Reminding Test[55] and the Double Memory Test,[56] but these had too many items to be used as a screening test for memory impairment in dementia. The MIS was developed as a short screening test[25] and uses a controlled learning (ie, acquisition) format: a short delay followed subsequently by a free recall and then a cued recall of items not recalled during free recall. Such controlled learning assures attention, equal processing strategies, and deep semantic processing. The administration format of the MIS helps with encoding specificity to improve retrieval by using the same cues for learning (acquisition) and retrieval.[25] Therefore, MIS can discriminate if decreased recall is because of impaired memory and not poor attention or different processing strategies. Studies in healthy volunteers that used scopolamine, an ACM used for motion sickness, noted impairments in learning acquisition, as well as free and delayed verbal recall.[57-60] Moreover, studies of the impact of ACM or those with anticholinergic properties (including benztropine and trihexyphenidyl) on memory in persons with schizophrenia and geriatric patients also reveal that ACM impair verbal learning and recall, and semantic organization, among other cognitive domains.[48-52,61] The large treatment effect (Hedges g = 1.35) showing improvement in verbal memory when ACM were tapered or discontinued among our patients whose baseline scores reflected memory impairment on the MIS scale is encouraging but requires replication because our sample was small. Nevertheless, if replicated, the MIS could serve as a screening and a treatment change assessment tool for ACM-induced memory impairment. Moreover, the relative ease of using the MIS makes it an attractive tool for routine clinic adaptation.

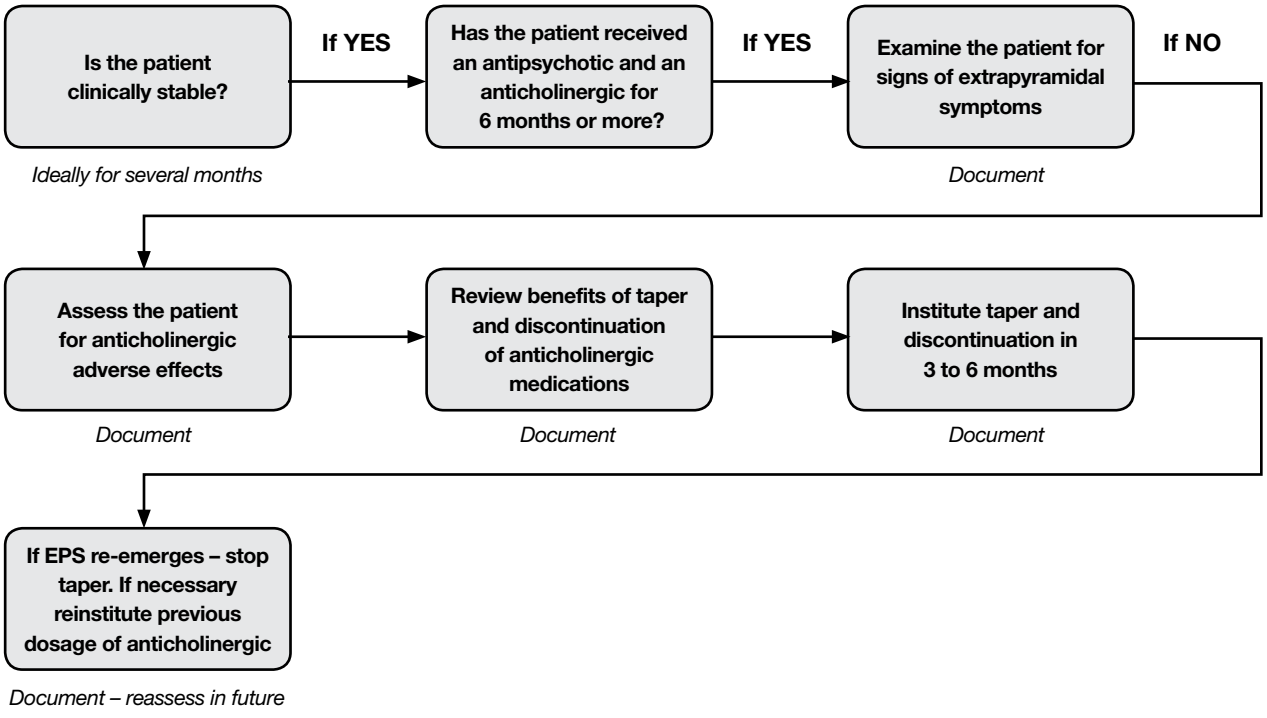
It is important to remember that several medications used in psychiatry and medicine in general have potent anticholinergic properties but are not classified primarily as ACM (eg, several antipsychotic and antidepressant drugs, antihistamines, furosemide, ranitidine,

metoprolol, and warfarin, among others).[23,52,62-64] Therefore, anticholinergic burden, especially in patients with psychiatric disorders, can quickly accumulate to well beyond an ACB scale score of 3, which is considered clinically relevant in geriatric patients and those at risk of cognitive impairment, such as patients with SMI.[23] Moreover, ACM have peripheral and CNS adverse effects, and in extreme cases, these agents can induce anticholinergic toxicity and delirium.[23,38] Curiously, ACM discontinuation studies in schizophrenia rarely report on improvements in peripheral anticholinergic adverse effects such as dry mouth, blurred vision, constipation, urinary retention, and tachycardia, which can in turn be associated with adverse clinical outcomes, including nonadherence to treatment. Deprescribing ACM in our pilot[22] and current project led to a 30% to 40% reduction in ACB scores as well as robust improvements in peripheral anticholinergic adverse effects. Future work could determine if these improvements with ACM discontinuation lessen the need for laxatives, stool softeners, or mouth moisteners and improve other clinical outcomes associated with peripheral anticholinergic adverse effects.

Who might be a candidate for deprescription of ACM? What tools, resources, and medication considerations might support the prescribing clinician and patient undertaking such medication optimization strategies? As noted in **FIGURE 3**, it is best to consider patients with SMI who are clinically stable for a reasonable period of time for deprescription of ACM. The WHO consensus statement states ACM should be considered for "short-term" use, without defining the duration of use. ACM discontinuation studies have used varying minimum durations of ACM and antipsychotic use; examples include 6 months,[22,65] 1 year,[21,29] and 2 years.[19] It would be prudent to obtain a history of EPS, and then examine patients for EPS; if none is evident, we would recommend engaging the patient in a conversation about adverse effects associated with ACM while simultaneously reviewing the benefits of taper and discontinuation of these medications. The use of the ACB,[23] PASS version 2.0, and the MIS[25] might not be easy to implement in busy clinics with 15-minute "med-check" appointments. However, if clinical pharmacists or staff support are available, we would recommend educating and training these team members on ACM deprescription and use of the scales noted above. The knowledge and use of such scales by physicians and staff might assist in measuring and documenting changes in both peripheral and CNS adverse effects of ACM before and after taper and discontinuation. In our experience, these activities typically engage the triad of prescriber, supporting health care professional, and patient in striving towards the same shared decision-making goal, ie, deprescription of ACM. After the patient agrees, monitoring the taper and discontinuation of ACM with more frequent phone and/or in-person visits is advisable. We would recommend, in most instances, a gradual taper of ACM over several weeks to months. Documenting the deprescription effort (ie, engagement, examination for EPS, ACM adverse effects assessments, memory screening tools) is recommended. Finally, a few patients likely will require ACM for extended periods of time when EPS recur. A switch to an antipsychotic agent with inherent anticholinergic properties or medications with a low risk of EPS might be appropriate, but the potential risk of destabilizing the patient's mental status should be considered. Similarly, a more obvious strategy to decrease EPS is to lower the dosage of the offending EPS-inducing antipsychotic medication, but this could lead to psychiatric decompensation and might not be feasible. When clinically appropriate, substituting amantadine for benztropine or trihexyphenidyl might lower anticholinergic burden.[6,35] Targeted cognitive training could be a therapeutic option to attenuate the ACB burden in severely disabled patients with SMI whose ACM cannot be deprescribed.[66] Finally, although acute antipsychotic-induced akathisia often is treated with anticholinergic agents, this approach is of limited utility. Medications with stronger evidence of efficacy for acute akathisia include beta blockers and benzodiazepines.[2]

Who might not be a good candidate for deprescription of ACM? Patients with a recent history of antipsychotic-induced dystonias, oculogyric crisis, severe tremors and rigidity, severe akathisia responsive to anticholinergics, and/or those who are not clinically stable likely are not good candidates for deprescription of ACM. Patients who are not clinically stable might be undergoing antipsychotic medication adjustments in terms of dosage and/or are switching agents, and those activities might be more of a priority than ACM deprescription. First-episode, antipsychotic-naïve, or early-course illness patients with schizophrenia might be especially sensitive to D2-blocking drugs, especially FGAs but also a few SGAs, and therefore might develop severe EPS, such as oculogyric crisis, other dystonias,

FIGURE 3
Clinical guide to deprescribing anticholinergic medications for antipsychotic-induced extrapyramidal symptoms



EPS: extrapyramidal symptoms.

severe akathisia, and parkinsonian features. If ACM are needed, it might be best to wait for an extended period of clinical stability (eg, 1 year) before considering ACM deprescription.

Limitations

This was a QI project with a small sample, and not a prospective random assignment study. We did not use formal scales for EPS or psychopathology that could have provided more measurable clinical information, and we did not measure serum anticholinergic levels. Using a small group and a problem-based learning, continuing education format, we were able to disseminate the successful results of the previous QI project[22] to a group of prescribers, and this led to deprescription of ACM among nearly 1 in 4 targeted patients with SMI without referral to the clinical pharmacists. This learning format might be especially useful when deprescription strategies are scaled to an audience of prescribers in large health care organizations, but it does limit the ability to collect outcomes data. A prospective, random assignment, parallel-group study with a more substantial sample size that includes blinded assessments of objectively rated scales could minimize selection and other biases emerging from the lack of a control group and could provide more definitive answers.

CONCLUSIONS

The results of this QI project highlight that regardless of patient demographics or type of antipsychotic

medication prescribed, patients can decrease the dosage or stop ACM previously prescribed for EPS symptoms. Discontinuing or decreasing benztropine or trihexyphenidyl dosage led to significantly improved clinical outcomes and patient quality of life. Therefore, physicians and other prescribing clinicians should carefully consider deprescribing long-term ACM in clinically stable patients with SMI. A patient-centered approach that includes patient education and shared decision making, the use of clinical scales to engage patients and measure improvements, and documentation in the medical record is ideal. Moreover, a slow taper and discontinuation of ACM over weeks to months generally is recommended. Finally, a multidisciplinary, collaborative effort with clinical pharmacists, therapists, and other patient care clinicians, when available, could be impactful for the scaling and success of such QI initiatives in large health care organizations. ■

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