Reducing Anticholinergic Medication Burden in Patients With Psychotic or Bipolar Disorders

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ABSTRACT

Objective: Anticholinergic medications are prescribed to treat extrapyramidal side effects (EPS) associated with antipsychotics. Anticholinergic medications cause several side effects and can often be withdrawn during the maintenance phase of antipsychotic treatment without EPS reemergence. The purpose of this quality improvement (QI) project was to reduce anticholinergic medication burden and improve quality of life in patients with severe mental illness.

Methods: Patients with *DSM-IV-TR*–diagnosed schizophrenia, schizoaffective disorder, and bipolar disorders in an outpatient psychiatric clinic who were prescribed benztropine were identified, screened for anticholinergic side effects by the treating psychiatrist, and referred to an on-site clinical pharmacist for a comprehensive medication review. Anticholinergic side effects, cognitive impairment, and impact on quality of life were assessed using a Likert scale. Recommendations for potential medication changes were discussed with the prescriber. Initial and follow-up assessments were conducted over 1–8 months to identify improvements in side effects and quality of life.

Results: Twenty-nine patients were assessed from November 2014 to December 2015. Patients were receiving from 1 to 6 medications with anticholinergic properties (median = 3 medications). Of the 29 patients, 19 were recommended for a medication change, with 13 having 1 or more anticholinergic medications discontinued and 6 having the dose decreased. A significant reduction in anticholinergic side effects and improvements in memory and quality of life were observed for these patients ($P \leq .05$).

Conclusions: In this interdisciplinary, collaborative QI project, patients whose anticholinergic burden was reduced experienced a significant improvement in side effects, memory, and quality of life.

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Antipsychotic medications represent the basis of current treatment for schizophrenia and related psychotic disorders. To date, all approved antipsychotics antagonize postsynaptic dopamine receptors to varying degrees, inducing an imbalance between the inhibitory dopaminergic and excitatory cholinergic neural systems in the striatal brain. Dopaminergic antagonism in subcortical areas of the brain produces extrapyramidal symptoms (EPS).[1] EPS are characterized by parkinsonian features, which may manifest acutely as dystonia or akathisia or subacutely as tremors, rigidity, bradykinesia, akathisia, and diminished arm swing. All antipsychotic medications carry the risk of EPS. The first-generation, high-potency antipsychotics (eg, haloperidol and fluphenazine) have a higher risk, and second-generation antipsychotics (eg, clozapine and quetiapine) pose a lower risk.[2]

In Parkinson's disease, anticholinergic medications are used to restore the balance between the dopaminergic and acetylcholinergic dysfunction. Similarly, in psychiatric practice, anticholinergic medications are prescribed to treat emergent antipsychotic-related EPS or to prevent medication-induced parkinsonism and dystonias among those at high risk.[3–4] Anticholinergic medications can have troublesome side effects, including dry mouth, dry eyes, constipation, cognitive dulling, blurred vision, or tachycardia, due to their antagonistic actions at the muscarinic receptors peripherally or centrally, and multiple anticholinergic medications can have additive effects.[5–8] Anticholinergic medications have also been shown to impair memory and cognition,[9–12] potentially worsening extant cognitive dysfunction, a feature closely linked to functional disability in schizophrenia.[13–18] Furthermore, long-term anticholinergic administration has been associated with worsening positive symptoms of schizophrenia, tardive dyskinesia, drug-drug interactions, polypharmacy, and medication nonadherence as well as rehospitalization and, ultimately, diminished quality of life.[19–23] Certain antipsychotics, such as olanzapine and clozapine, have anticholinergic properties, which should be taken into consideration when prescribing these medications.[24]

Clinical guidelines[23,25,26] recommend against prophylactic and long-term use of anticholinergic medications for EPS, but this is often overlooked in clinical practice.[27] While these medications may be needed early in the course of antipsychotic treatment, they can usually be withdrawn over time without EPS recurrence. A growing body of evidence suggests that discontinuing long-term use of anticholinergic agents can lead to improvements in memory, anticholinergic side effects, and quality of life.[28–31] In addition, clinicians may choose antipsychotics with no or minimal EPS risk, including but not limited to aripiprazole, lurasidone, and quetiapine, to further prevent anticholinergic side effects.[24]

Clinical Points

- Physicians should periodically reassess the need for long-term anticholinergic medications for prevention or treatment of extrapyramidal symptoms in patients with serious mental illness.
- Providers should also develop a patient-centered strategy to discontinue anticholinergic medications, taking into account side effects and impact on quality of life.
- Physicians must anticipate the need for additional counseling, including in between clinic visits, to support patients in the implementation of the anticholinergic tapering process.

This article describes a pilot quality improvement (QI) project involving a multidisciplinary initiative to diminish anticholinergic burden in an outpatient clinic serving patients with severe mental illness (SMI). The primary goal was to improve clinical outcomes and quality of life in patients prescribed anticholinergic medications by reducing side effects and medication burden.

METHODS

This pilot project was an interdisciplinary collaboration between the outpatient psychiatrists and clinical pharmacists at Western Psychiatric Clinic and Institute (WPIC) of UPMC (University of Pittsburgh Medical Center). The QI project was approved by the UPMC Quality Improvement Review Committee. Informed consent is not required for quality improvement projects at UPMC. Following approval, the QI initiative was presented to all attending psychiatrists and residents at the Comprehensive Recovery Services (CRS) Clinic of WPIC.

Setting and Patients

The CRS ambulatory clinic served as the project site. CRS is a specialty clinic that treats adult patients 18 years and older with SMI, including *DSM-IV-TR*–diagnosed schizophrenia, schizoaffective disorder, and bipolar disorders. As part of the comprehensive care model, all services are co-located in the same building. Patients have access to their psychiatry clinical team (psychiatrists, psychiatric residents, and therapists), a clinical laboratory, and a dispensing pharmacy that provides clinical pharmacy services and supports a long-acting injectable antipsychotic and clozapine clinic. Clinical pharmacists serve as an integral part of the treatment team by providing comprehensive medication management, making recommendations to ensure safe and effective medication use, and providing medication and disease state education. Initially, patients were identified through a pharmacy-generated list which indicated that 61 clinic patients were taking benztropine for a minimum of 3 months. Psychiatrists were given the list of patient names and were asked to refer to a clinical pharmacist patients who might benefit from a pharmacy consultation and possible reduction of anticholinergic medication. Some psychiatrists referred patients who were taking anticholinergic medications other than benztropine for anticholinergic burden reduction, and these patients were included in this study as well.

Measures

Anticholinergic burden was assessed using the Anticholinergic Cognitive Burden (ACB) scale developed by Boustani et al,[32] which categorizes medication severity of inducing anticholinergic side effects in patients. The ACB scale is widely used and validated.[32,33] Medications with no anticholinergic activity are assigned a score of zero. Medications for which there is evidence of antagonist activity at muscarinic receptors are given a score of 1. Medications for which there is evidence of clinical anticholinergic effects from the literature, manufacturer's information, or expert opinion are given a score of 2, and those with the potential to cause delirium are scored as 3. The authors concluded that, for each individual, a total score of 3 or more on the ACB scale was clinically significant.[32]

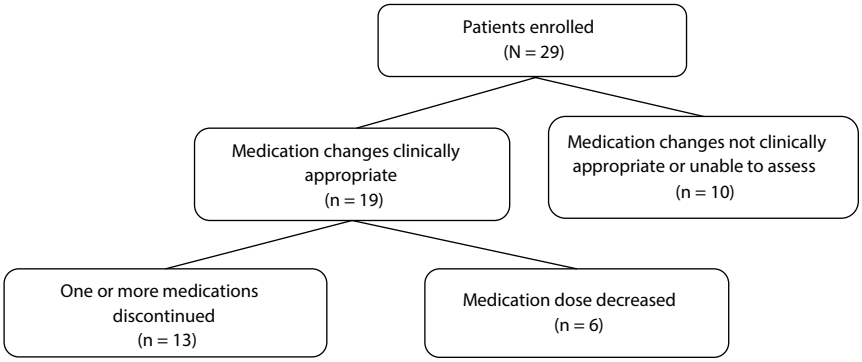
Anticholinergic symptoms and their impact on quality of life were assessed using the Pittsburgh Anticholinergic Symptom Scale (PASS), a clinical tool used previously in our system that has not yet been validated in research trials (see eAppendix 1). Patients completed the PASS with assistance, utilizing a 0–10 Likert scale to estimate the severity of their anticholinergic symptoms (dry mouth, blurred vision, hot dry skin, difficulty urinating, constipation, fast heartbeat), confusion, or memory problems and their impact on quality of life. The "5-word recall" test from the Montreal Cognitive Assessment (MoCA)[34] was used to assess cognitive impairment.

Intervention and Statistical Analysis

In the CRS clinic, benztropine is the anticholinergic medication prescribed for EPS by most psychiatrists. Benztropine is highly anticholinergic[32] and has been used as a standard to compare equivalency of other anticholinergic medications.[35] Thus, for this pilot project, patients taking benztropine for an extended period of time were considered at highest risk of anticholinergic side effects. A pharmacy-generated report was used to identify patients prescribed benztropine for at least 3 months. These patients were screened for side effects related to anticholinergic medications by their psychiatry team during routine visits. Patients who reported anticholinergic side effects were then referred to a clinical pharmacist for further evaluation. During the initial consultation, the clinical pharmacist conducted a comprehensive medication review, including medication reconciliation, to identify all possible anticholinergic medications and evaluate anticholinergic side effects and their impact on quality of life.

Recommendations for potential medication changes were discussed with the patients and prescribers. When clinically appropriate, medications were tapered and/or discontinued by prescribers over time. Follow-up assessments by clinical pharmacists were conducted in person and via telephone. The PASS was readministered at follow-up visits to identify

Figure 1. Enrollment and Outcomes of Patients Receiving Anticholinergic Medications



potential improvements in side effect burden and quality of life secondary to reduction in anticholinergic medications. Patients were also monitored for reemergence of EPS. The Wilcoxon signed rank test was used to compute statistically significant changes in the outcome measures.

Table 1. Demographics and Baseline Characteristics

Variable	Value
Patients, N	29
Female, % (n)	69 (20)
Age, mean (range), y	54 (30–71)
No. of anticholinergic medications at baseline, median (range)	3 (1–6)

RESULTS

Over a 13-month period (November 2014 to December 2015), physicians referred a total of 29 patients to a clinical pharmacist who, after the initial patient assessment, made recommendations to the treatment teams. Of the 29 patient referrals, 19 patients were identified as clinically appropriate for potential anticholinergic medication change (Figure 1). For the 10 remaining patients, the psychiatry teams determined that discontinuing or lowering the dose of a medication could negatively impact patient outcomes due to the risk of either EPS exacerbations or psychiatric destabilization.

Table 1 describes demographics and baseline characteristics of participants. Of the 29 patients enrolled, 20 (69%) were female and 9 (31%) were male. The mean age was 54 years (range, 30–71). Participants were taking from 1 to 6 medications with anticholinergic properties (with a median of 3 medications per patient). In addition to benztropine, other medications with anticholinergic properties included antipsychotics, antidepressants, antihistaminic agents, anticholinergic agents for urinary incontinence, and antihypertensive agents. All patients assessed had an anticholinergic burden score of 3 or more, since all were receiving benztropine, which by itself scores a 3 on the ACB scale. Supplementary eTable 1 lists specific anticholinergic medications and their respective ACB scale score, at baseline and post-intervention, for the 19 patients who had medication changes.

Of the 19 patients identified by the treatment team to be clinically appropriate for a medication change, 13 had at least 1 anticholinergic medication discontinued and 6 had dose decreases. Tapering schedules were determined collaboratively with the psychiatrist. Total tapering time ranged from 1 to 8 months with medication changes typically requiring 2–3 months. The patients attended the clinic at different time intervals. Benztropine was the most commonly discontinued medication, with 17 prescriptions recorded at baseline and only 7 prescriptions continued post-intervention (Figure 2). Six patients began to experience EPS once the benztropine was tapered, and in these patients the medications were decreased to the minimum effective dose rather than discontinued. Figure 2 illustrates changes in other anticholinergic medications, which included metoprolol, hydroxyzine, amantadine, quetiapine, and ranitidine, though many of these were not initially targeted.

The anticholinergic burden score is the sum of the score for each anticholinergic medication on the ACB scale. The median ACB scale score was 7 (range, 3–14) at baseline and 5 (range, 0–13) post-intervention (Table 2). Patient-reported scores on a 0–10 Likert scale for each anticholinergic side effect (dry mouth, blurred vision, hot dry skin, difficulty urinating, constipation, fast heartbeat, confusion or memory problems) were added to obtain the PASS score. The median PASS score was 29 (range, 2–60) at baseline and 14 (range, 2–48) post-intervention. The median memory recall score was 4 (range, 2–5) at baseline and 5 (range, 3–5) post-intervention. Impact of anticholinergic burden on quality of life was assessed on a 0–10 Likert scale, and the median score was 5 (range, 2–10) at baseline and 3 (range, 0–10) post-intervention. Using the Wilcoxon signed rank test, we found a significant reduction in anticholinergic burden as well as significant improvements in side effects, memory, and quality of life ($P \leq .05$) at the end of the intervention (Table 2).

DISCUSSION

This pilot study suggests that it is possible to reduce anticholinergic burden, diminish or eliminate troublesome

Figure 2. Anticholinergic Medication Changes From Baseline to Post-Intervention

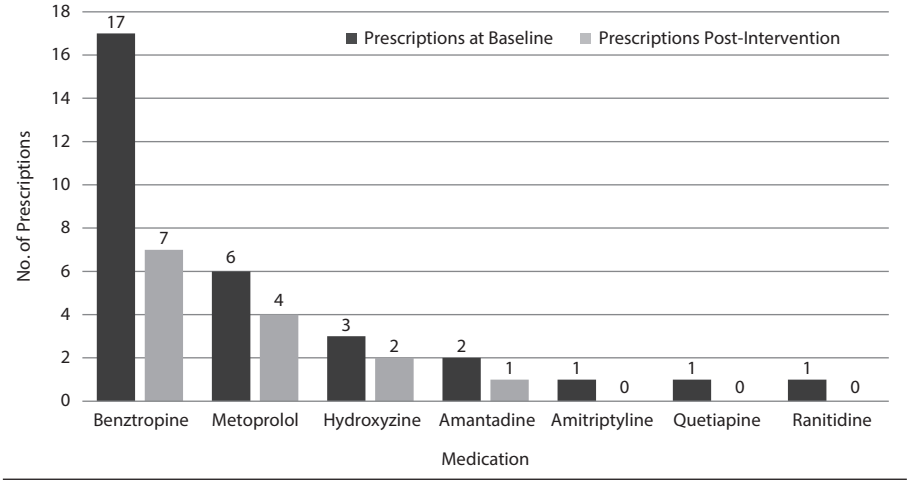


Table 2. Changes in Anticholinergic Burden and Patient-Reported Anticholinergic Symptoms After Intervention[a] (n = 19)

Variable	Baseline Median (Minimum–Maximum)	Post-Intervention Median (Minimum–Maximum)	*W* Value[b]
No. of anticholinergic medications	3 (1–6)	2 (0–5)	0
Anticholinergic burden score	7 (3–14)	5 (0–13)	0
PASS score[c]	29 (2–60)	14 (2–48)	11.5
Memory recall score[d]	4 (2–5)	5 (3–5)	0
Quality of life impact score	5 (2–10)	3 (0–10)	6

[a]Interventions consisted of 1 or more anticholinergic medications being discontinued (n = 13) or dose decreases of anticholinergic medications (n = 6).
[b]All *W* values (Wilcoxon signed-rank test) were less than the critical median values and therefore significant at $P \leq .05$.
[c]Sum of 7 patient-reported anticholinergic symptoms on the Pittsburgh Anticholinergic Symptom Scale (PASS); excludes memory recall score and quality of life impact score, as these were evaluated separately.
[d]A 5-word recall test for cognitive impairment.

side effects associated with anticholinergic medications, and improve quality of life in patients with SMI by routinely reevaluating medication regimens and instituting thoughtful medication changes. It is pertinent to note that among the elderly, every 1-point increase in the ACB scale total score translates to a 0.33-point decline in Mini-Mental State Examination score over 2 years and also to a 26% increase in the risk for mortality.[36] Moreover, each anticholinergic medication that a patient takes may increase risk of cognitive impairment by 46% over 6 years.[37] Our study found a median 2-point reduction in the ACB scale total score in this small sample, and the median number of anticholinergic medications was decreased from 3 to 2 within a few months. The side effects typically associated with anticholinergic medications (eg, dry mouth, constipation, difficulty urinating, blurred vision, fast heartbeat, dry skin) declined by over 50% following a reduction or elimination of anticholinergic medications. Recall memory scores also improved post-intervention. Unsurprisingly, these improvements in the ACB scale and PASS scores translated to patients' reporting improved quality of life.

Limitations of this study include a small sample size and selection bias, as patients who were successfully referred to the clinical pharmacists were more likely to engage with suggested modifications in medication regimens. The scope of this pilot study was limited, as patients were initially screened for possible inclusion by chronic prescription usage of benztropine only rather than multiple other anticholinergic medications. Anticholinergic assays were not obtained, as this would have been overly invasive for the purpose of this QI study. In addition, the absence of validated scales for assessment of quality of life and cognition could have limited the results. However, the Likert scale for quality of life and the 5-word recall test for cognition allowed for ease of administration during follow-up appointments as well as ease of replicability in a clinical setting. Finally, this study, with its focus on quality improvement in an ambulatory clinic, was unblinded and nonrandomized and lacked a control group.

Strengths of this study include its pragmatic design and multidisciplinary approach. Another key point to highlight is the educational value of this project to the clinic. In-services and one-on-one interventions were provided to emphasize the need for continuous evaluation of the additive effects of multiple medications and the effect of anticholinergic burden on patient quality of life and clinical outcomes. The scales deployed were easy to use and required little to no training to implement. The study also emphasizes the benefits of interdisciplinary collaboration between clinical pharmacists and psychiatrists in identifying and addressing anticholinergic burden in an SMI population. Clinical pharmacists were able to work closely with patients in between scheduled physician appointments and collaborate with outside providers. They provided close follow-up, monitored for adverse effects, and promoted patient adherence. While clinical pharmacy involvement was an asset to this

project, sites lacking clinical pharmacists may still develop similar models with the aim to reduce anticholinergic burden and improve patient quality of life. Engagement of other support staff such as nurses or a slower reduction in anticholinergic medications may be required in absence of this collaboration.

Patients with SMI, particularly the elderly and those with comorbid medical conditions, are at high risk for anticholinergic side effects.[32,36–38] These patients should be carefully screened to prevent worsening complications of urinary obstruction, constipation, glaucoma, and cardiac disease secondary to high anticholinergic burden. Cognitive deficits are not uncommon to schizophrenia or bipolar disorders; therefore, patients should also be assessed for neurocognitive impact of anticholinergic agents. Such agents should be avoided, when possible, in patients with dementia and intellectual disability. Patients prescribed anticholinergic medications for side effects like clozapine-induced sialorrhea or overflow urinary incontinence also require careful monitoring and may benefit from switching to other agents with less significant side effect burden (eg, topical atropine drops for sialorrhea), and lifestyle modifications. Patients on stable doses of long-term antipsychotic agents with concomitant anticholinergic medications prescribed for prevention or treatment of EPS should be periodically evaluated for potential dose reduction or elimination of the latter medications, even in the absence of clear anticholinergic side effects.

Patients with ongoing acute EPS, including drug-induced parkinsonism and dystonias, may not be good candidates for targeted elimination of anticholinergic medications. Patients with tardive dystonias who respond to anticholinergic medications may also require continued use of these agents. Such patients may benefit from switching to atypical antipsychotics with less EPS risk, although some of these agents, in particular clozapine and olanzapine, also possess a significant anticholinergic burden. Clinical risks and benefits must be carefully weighed before a medication change is made. Patients on long-term tricyclic antidepressants for treatment-resistant depression, for instance, may not do well with a switch to selective serotonin reuptake inhibitors. Moreover, patients receiving clozapine for treatment-refractory schizophrenia often decompensate when switched to other medications. Anticholinergic medications, especially those with antihistaminergic effects, are often used to treat agitation, anxiety, and insomnia. Withdrawal of these medications, especially when performed abruptly, can lead to an exacerbation of these symptoms and even precipitate cholinergic rebound, which can include agitation, diarrhea, vomiting, lacrimation, tachycardia, insomnia, and withdrawal movement disorders.[39–41] In these cases, and anytime a medication change is made, close monitoring, education, and reassurance are instrumental in ensuring positive outcomes to identify and prevent decompensation. The role of the clinical pharmacists was particularly valuable, as they provided monitoring and education through frequent contact with patients, both face-to-face and via telephone.

CONCLUSION AND FUTURE DIRECTIONS

In this pilot study, reducing anticholinergic burden resulted in improvements in anticholinergic symptoms, memory, and quality of life in patients with SMI. The multidisciplinary collaboration between psychiatry and pharmacy allowed for close monitoring and an additional layer of care in this vulnerable patient population. This study outlines a unique model that may be applied in clinical practice in some but not all settings. Further prospective evaluations of patients with mental illness are needed to determine the impact of reducing anticholinergic burden on patient outcomes and antipsychotic medication adherence. Areas for future investigation particularly relevant to the clinician include the rate of anticholinergic taper and the moderating effects each antipsychotic may have on the outcomes of anticholinergic cognitive burden reduction. A randomized controlled trial of benztropine continuation versus discontinuation in the era of second-generation antipsychotics would also be an interesting avenue of research.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Reducing Anticholinergic Medication Burden in Patients With Psychotic or Bipolar Disorders

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List of Supplementary Material for the article

1. **eAppendix 1** Pittsburgh Anticholinergic Symptom Scale (PASS)

2. **eTable 1** Anticholinergic Medications

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

eAppendix 1. Pittsburgh Anticholinergic Symptom Scale (PASS)[1]

Patient Name	**Visit 1**	**Visit 2**
MRN		
Age		
Gender		
Anticholinergic Medications/ACB Score		
Total Anticholinergic Burden Score (ACB Score)		
Patient Reported Dry Mouth 0 (Never) – 10 (Every Day)		
Patient Reported Blurred Vision 0 (Never) – 10 (Every Day)		
Patient Reported Dry Skin 0 (Never) – 10 (Every Day)		
Patient Reported Difficulty Urinating 0 (Never) – 10 (Every Day)		
Patient Reported Constipation 0 (Never) – 10 (Every Day)		
# BM/week		
Patient Reported Fast Heartbeat 0 (Never) – 10 (Every Day)		
Patient Reported Memory Problems 0 (Never) – 10 (Every Day)		
Five Word Recall (__/5 words remembered after 5 minutes)		
Patient Reported Impact on Quality of Life 0 (no interference with daily function) – 10 (significant interference with daily function)		

[1]The PASS is reprinted with permission from K. N. R. Chengappa

Supplementary eTable 1. Anticholinergic Medications (N=19)				
Generic Medication Name	ACB Score	Prescriptions at Baseline	Prescriptions Post-Intervention	Difference
Amantadine	2	2	1	1
Amitriptyline	3	1	0	1
Aripiprazole	1	1	1	0
Atenolol	1	1	1	0
Benztropine	3	17	7	10
Bupropion	1	1	1	0
Clozapine	3	7	7	0
Digoxin	1	1	1	0
Diphenhydramine	3	1	1	0
Doxepin	3	1	1	0
Furosemide	1	2	2	0
Haloperidol	1	5	5	0
Hydroxyzine	3	3	2	1
Metoprolol	1	6	4	2
Oxybutynin	3	1	1	0
Paliperidone	1	3	3	0
Perphenazine	3	1	1	0
Quetiapine	3	1	0	1
Ranitidine	1	1	0	1
Risperidone	1	2	2	0
Solifenacin	3	1	1	0
Trazodone	1	3	3	0
Trospium	3	1	1	0
Venlafaxine	1	1	1	0