Maryland
DEPARTMENT OF HEALTH

PHARMACY
News & Views

SPRING 2025

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Find details at https://health.maryland.gov/mmcp/pap/Pages/pharmacists-professional-services.aspx and the Maryland Department of Health Advisory No. 272.

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Anticholinergic Burden in Schizophrenia Treatment

Patients being treated for mental health conditions are more likely to experience significant drug interactions than patients receiving treatment for somatic conditions due to the wide-ranging effects of central nervous system (CNS) medications.[1,2] Although polypharmacy may be necessary for some patients, it does not come without risks. Examples of polypharmacy as well as the potential risks to a patient can often be seen in the treatment of schizophrenia.[2,3]

American Psychiatric Association (APA) guidelines recommend pharmacotherapy for schizophrenia to treat the patient's reported positive, negative, and cognitive symptoms along with discussion about potential side effect profiles. When selecting a medication, it is important to take into account various factors including past responses to treatment, concurrent health conditions, and potential medication interactions. Nonpharmacological treatments like psychotherapy are recommended in conjunction with pharmacotherapy for optimal patient outcomes.[4]

In the United States, schizophrenia prevalence is estimated at 0.7% of individuals.[5] Symptoms of schizophrenia are commonly described as positive, negative, and cognitive. Positive symptoms include auditory or visual hallucinations, delusions, and paranoia. Negative symptoms of schizophrenia may present as loss of motivation, interest or enjoyment; withdrawal from social interactions, decreased speech and difficulty showing emotions. Catatonia may occur in rare cases. Difficulty paying attention, making decisions, and remembering information are cognitive symptoms also associated with schizophrenia.[4-6]

Traditionally, schizophrenia has been treated with medications which target dopamine receptors, particularly D2. Newer agents are being developed to utilize different mechanisms, aiming to improve efficacy across all symptom types and minimize side effects. First and second-generation antipsychotics (FGAs and SGAs) are effective in treating the positive symptoms of schizophrenia but have limited efficacy on the negative and cognitive symptoms.[4-6]

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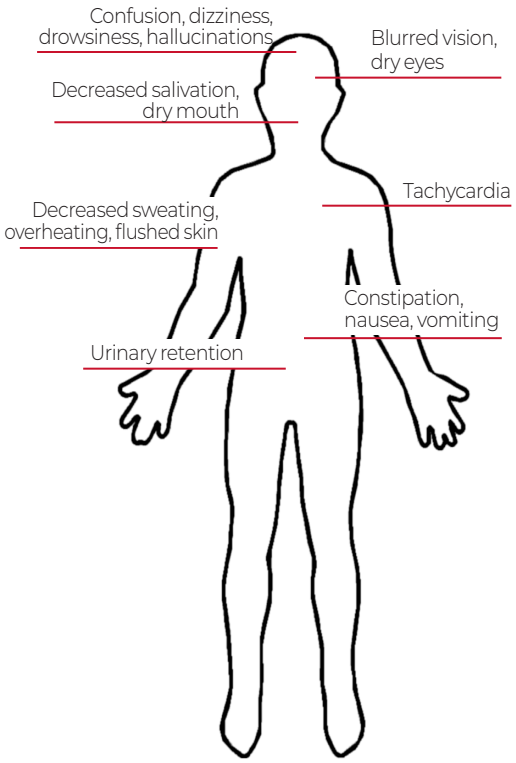
Anticholinergic Burden in Schizophrenia Treatment *(continued)*

COMMON ANTICHOLINERGIC ADVERSE EFFECTS

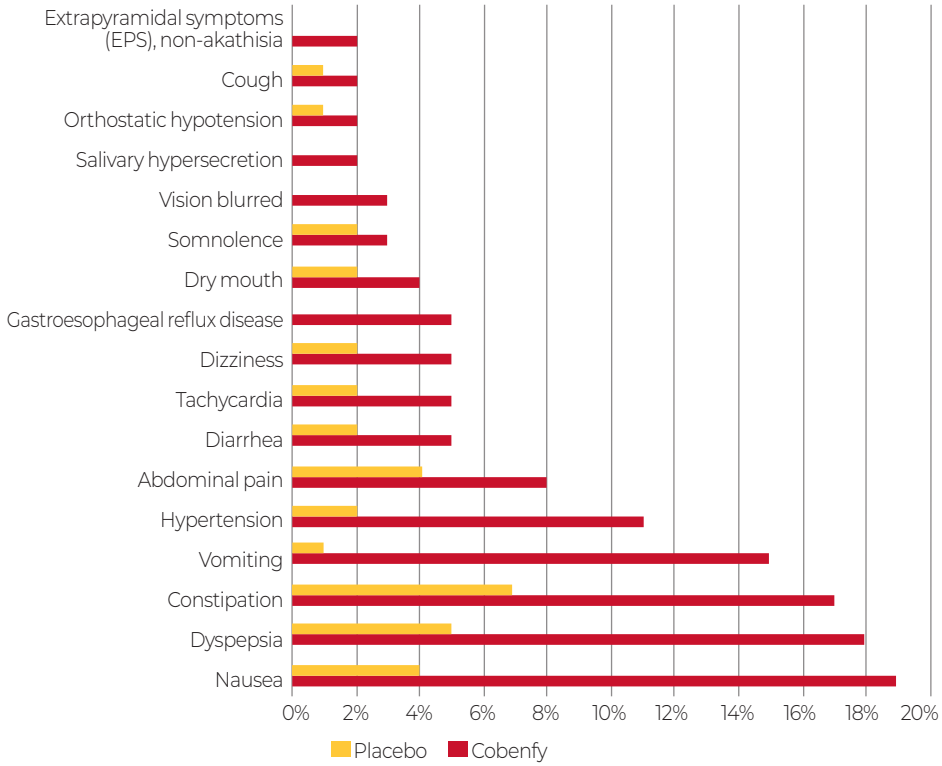


Common adverse effects associated with FGAs and SGAs are extrapyramidal symptoms (dystonia, dyskinesia, parkinsonism, akathisia), weight gain, orthostatic hypotension, prolactin elevation, sedation, and QTc prolongation. SGAs also have some serotonin receptor activity, and the class has a Boxed Warning for increased mortality when used to treat dementia-related psychosis in elderly patients. Additionally, the low potency FGAs chlorpromazine and thioridazine as well as the SGAs clozapine and olanzapine have significant anticholinergic effects due to their affinity for muscarinic M1 receptors peripherally.[4]

A novel medication for schizophrenia, Cobenfy (xanomeline and trospium chloride), combines the central and peripheral M1 and M4 muscarinic agonist xanomeline with the peripheral M1 muscarinic antagonist trospium.[7] Cobenfy does not have the antipsychotic class boxed warning regarding increased mortality in patients with dementia-related psychosis and has not demonstrated significant changes in metabolic parameters during clinical trials.

There are currently no direct comparison studies with other antipsychotics, but several ongoing studies are investigating its efficacy when used for adjunctive treatment of schizophrenia, treatment of psychosis in patients with Alzheimer's disease, and in treating the negative symptoms of schizophrenia. Due to the muscarinic receptor activity of both xanomeline and trospium, Cobenfy has significant risk of anticholinergic side effects[7]. A summary of adverse effects seen in clinical trials as compared to placebo is shown below.

Adverse Reactions Reported in >2% of COBENFY-Treated Patients and Greater than Rate of Placebo in Two 5-week Schizophrenia Trials[7]



It is contraindicated in patients with urinary retention, moderate or severe liver disease, gastric retention, untreated narrow-angle glaucoma, or a history of hypersensitivity to Cobenfy or its components. Use of Cobenfy is not recommended in patients with mild hepatic impairment, moderate or severe renal impairment, and should be used with caution in patients with biliary disease, gastrointestinal obstructive disorders, or narrow-angle glaucoma.[7]

Cobenfy also poses a unique challenge when it comes to drug interactions. Drug interactions include with drugs eliminated by active tubular secretion, strong CYP2D6 inhibitors, sensitive substrates of CYP3A4 or P-glycoprotein, and antimuscarinic drugs. See chart for more information.[7,8]

Drug Category	Effects[8]	Medication Examples
Eliminated by active tubular secretion	Increase trospium plasma levels; Increase interacting medication plasma levels	Tenofovir, Cephalosporins, diuretics, dofetilide, penicillins, pramipexole[9]
Strong CYP2D6 inhibitors	Increase xanomeline plasma levels	Bupropion, fluoxetine, paroxetine, quinidine, terbinafine[8,10]
Sensitive substrates of CYP3A4	Increase interacting medication plasma levels	Buspirone, darunavir, dronedarone, eletriptan, eplerenone, ivabradine, lovastatin, simvastatin, sirolimus, lurasidone, quetiapine, tacrolimus[8,10]
Sensitive substrates of P-glycoprotein	Increase interacting medication plasma levels	Apixaban, colchicine, digoxin, fexofenadine[8,10]
Antimuscarinic medications	Cumulative anticholinergic adverse effects	Benztropine, diphenhydramine, oxybutynin[8]

Individuals with schizophrenia experience higher rates of co-occurring somatic health conditions such as cardiovascular disease, diabetes mellitus, hepatitis C and HIV infection, and liver disease among others[4]

An estimated one-half of patients diagnosed with schizophrenia also have co-occurring mental and/or behavioral health conditions such as anxiety, depression, and substance use disorders.[5] The cumulative effects of medications used to treat these conditions along with a medication addition, modification, or decrease in kidney or liver function could result in significant side effects for a patient. Monitoring of liver enzymes, bilirubin, and renal function tests like estimated glomerular filtration rate (eGFR) can be used to assess if a medication is still appropriate for a patient, although there may be other specific monitoring parameters depending on the particular medication(s). Anticoagulants, antivirals, and medications with narrow therapeutic windows such as digoxin and dofetilide should be of particular interest when reviewing a medication profile.

Prior to starting a new medication, the cumulative effects of the patient's full prescription regimen should be considered. In the treatment of schizophrenia, taking multiple medications with anticholinergic activity may contribute to anticholinergic burden-related side effects. Several online calculators exist for assessing patient anticholinergic burden and can offer some guidance in therapy management, however there is no universally accepted scale. If a medication with significant anticholinergic effects such as Cobenfy is used, consider tapering off another high-risk medication. Additionally, the patient or caregiver should be educated on adverse effects and self-monitoring including cognitive dysfunction, constipation, delirium, dizziness, dry mouth, dyspepsia, falls, nausea, tachycardia, and urinary retention.[7,8,11] Several schizophrenia pipeline agents have mechanisms of action that target muscarinic receptor(s), making cholinergic drug interactions and adverse effects more likely in the coming years in this patient population.

Many medications may contribute to a drug therapy problem; however, the negative impacts of polypharmacy drug interactions are particularly pronounced with mental health medications and in older patients with psychiatric illness.[1,2] Pharmacists are essential in ensuring safe and appropriate medication use for Maryland Medicaid patients and are encouraged to take a proactive role in reviewing prescriptions for appropriateness, alerting the prescriber to significant drug interactions and educating the patient about self-monitoring parameters. Patients with several different prescribers benefit from having one pharmacy that fills all their medications to ensure thorough prospective drug use review and facilitate interprofessional collaboration and communication. Community pharmacists may also provide patients with recommendations for management of common anticholinergic symptoms like laxatives or increased fiber for constipation or xylitol lozenges and increased fluid intake for dry mouth.[12]

Maryland
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Aruna Miller, Lt. Governor

Meena Seshamani, MD, PhD, Secretary

OFFICE OF PHARMACY SERVICES

300 West Preston Street
Baltimore, MD 21201

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CONTACT NUMBERS

- **Conduent Technical Assistance**
  800-932-3918
  24 hours a day, 7 days a week
- **Maryland Medicaid Pharmacy Access Hotline**
  833-325-0105
  Monday-Friday, 8:00 am - 5:00 pm
- **Kidney Disease Program**
  410-767-5000 or 5002
  Monday-Friday, 8:00 am - 5:00 pm
- **Breast and Cervical Cancer Diagnosis and Treatment**
  410-767-6787
  Monday-Friday, 8:00 am - 4:30 pm
- **Maryland AIDS Drug Assistance Program**
  410-767-6535
  Monday-Friday, 8:30 am - 4:30 pm
- **Peer Review Program**
  855-283-0876
  Monday-Friday, 8:00 am - 6:00 pm

Atypical Antipsychotic Agents: 30-day Emergency Supply

When the prescriber is not available to obtain prior authorization for an antipsychotic medication that is non-preferred or second tier, the pharmacist can obtain a one-time only authorization to dispense up to a 30-day emergency supply. Do not let patients leave the pharmacy without medication if there is concern that the patient will be unwilling or unable to return at a later time that day after prior authorization is approved. To obtain authorization for an emergency supply of an antipsychotic, call Conduent Technical Assistance at 800-932-3918. During the 30-day window, the pharmacist must notify the prescriber of the need to obtain a PA before the prescription can be filled a second time and make a note for his or her records of the date, time and person contacted at the prescriber's office.

References

1. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: populations database analysis 1995-2010. BMC Med. 2015 Apr 7;13:74.
2. Wien K, Reibner P, Hefner G et al. Prevalence and solving strategies of drug-related problems in adult psychiatric inpatients-a systematic review. Front Psychiatry. 2024 Dec 4; 15:1460098.
3. Joshi YB, Thomas ML, Braff DL et al. Anticholinergic medication burden-associated cognitive impairment in schizophrenia. Am J Psychiatry. 2021 Sep 1;178(9):838-47.
4. American Psychiatric Association. Practice Guideline for the Treatment of Patients with Schizophrenia. 3rd ed. Washington, DC: American Psychiatric Association; 2020.
5. National Institute of Mental Health. Schizophrenia. https://nimh.nih.gov/health/statistics/schizophrenia (accessed 2025 Apr 23).
6. MedlinePlus. Schizophrenia. https://medlineplus.gov/schizophrenia.html (accessed 2025 Apr 23).
7. Cobenfy (xanomeline and trospium chloride) prescribing information. Princeton, NJ: Karuna Therapeutics Inc; 2024 Sep.
8. Cobenfy (xanomeline and trospium chloride) dosing guide. Princeton, NJ: Karuna Therapeutics Inc; 2024 Oct.
9. Wang K, Kestenbaum B. Proximal Tubular Secretory Clearance. Clin J Am Soc Nephrol. 2018 Feb 28; 13(8):1291-6.
10. Food and Drug Administration. For Healthcare Professionals | FDA's Examples of Drugs that Interact with CYP Enzymes and Transporter Systems. https://fda.gov/drugs/drug-interactions-labeling/healthcare-professionals-fdas-examples-drugs-interact-cyp-enzymes-and-transporter-systems (accessed 2025 Apr 23).
11. Ghossein N, Kang M, Lakhkar AD. Anticholinergic Medications. [Updated 2023 May 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. https://ncbi.nlm.nih.gov/books/NBK555893/
12. Am. College of Clinical Pharmacy. About clinical pharmacists. https://accp.com/about/clinicalpharmacists.aspx (accessed 2025 Apr 23).