August 30, 2019

Clinical Review Update: Concomitant Anticholinergic and Antipsychotic Use

Learning Objectives:

- Understand the role of anticholinergic medications in the prevention and treatment of antipsychotic-induced extrapyramidal symptoms (EPS).
- Describe factors that should be considered when deciding to initiate and/or continue the concomitant use of anticholinergic with antipsychotic medication therapy.

Key Points:

- Anticholinergic medications, including benztropine and trihexyphenidyl, are often prescribed to prevent or treat antipsychotic-induced EPS; however, the need for continued therapy with anticholinergics is not often reassessed and many patients continue to use these medications.
- The consensus among the medical community is that prophylaxis of EPS with anticholinergics is generally not indicated in patients receiving antipsychotics, in particular among patients who are prescribed second-generation antipsychotics.
- Long-term use of anticholinergic medications is associated with cognitive impairment and worsening of tardive dyskinesia, especially among persons 65 years of age or older.
- Among the 268,245 Medi-Cal beneficiaries with a paid claim for any antipsychotic medication during the measurement year, a total of 29,807 (11%) beneficiaries had concomitant use of anticholinergic medication during this period. Among this population, a total of 15,487 (6%) beneficiaries also had at least six paid claims for an anticholinergic medication during this same time period, suggesting long-term use of concomitant anticholinergic and antipsychotic medications.
- Concomitant use of anticholinergic medications was higher among the 23,191 Medi-Cal beneficiaries with at least one paid claim for a first-generation antipsychotic medication (n = 9,767; 42%), in comparison to the 260,655 Medi-Cal beneficiaries with paid claims exclusively for second-generation antipsychotic medications (n = 27,137; 10%).
- Continued use of anticholinergic medications should be re-evaluated in patients with controlled symptoms every three months.

Background

Anticholinergic medications, including benztropine and trihexyphenidyl, are often prescribed to prevent or treat antipsychotic-induced EPS, including tremor, rigidity, bradykinesia, and acute dystonia.[1] However, the need for continued therapy with anticholinergics is not often reassessed and many patients continue to use these medications for several years or even decades.[1] Prescribers may be reluctant to discontinue anticholinergics even when patients are prescribed second-generation antipsychotics, which are less likely than first-generation antipsychotics to induce EPS.[1-5]

Despite the widespread use of anticholinergic medications for prophylaxis and treatment of antipsychotic-induced EPS, there is a lack of systematic reviews and meta-analyses supporting this practice, and the long-term benefit of anticholinergic use has not been established.[1,6] In fact, several adverse effects have been reported from long-term use, including cognitive impairment and worsening of tardive dyskinesia, especially among persons 65 years of age or older.[5,7,8] The 2009 Schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations state that the prophylactic use of anticholinergics to reduce the incidence of EPS was not warranted in patients treated with second-generation antipsychotics but should be evaluated on a case-by-case basis for patients treated with first-generation antipsychotics.[9,10]

The consensus among the medical community is that prophylaxis of EPS with anticholinergics is generally not indicated in patients receiving antipsychotics and that anticholinergic use should be limited to when parkinsonism arises and when other measures, such as dose reduction, have failed.[11] As differences in the risk for EPS are correlated to the relative potency of antipsychotics, switching to antipsychotics with a lower propensity for EPS may also help limit or avoid the use of anticholinergics (Table 1).[9,10]

Table 1. General Ranking of Selected First- and Second-Generation Antipsychotics by Propensity for EPS[9,10,12-15]

High potency first-generation antipsychotics: Fluphenazine, haloperidol, pimozide, thiothixene, trifluoperazine	**Highest propensity for EPS**
Mid potency first-generation antipsychotics: Loxapine, perphenazine	
Second-generation antipsychotics: Paliperidone, risperidone	
Second-generation antipsychotics: Asenapine, cariprazine, lurasidone	
Low potency first-generation antipsychotics: Chlorpromazine, thioridazine	
Second-generation antipsychotics: Aripiprazole, brexpiprazole, olanzapine, ziprasidone	
Second-generation antipsychotics: Quetiapine, iloperidone, pimavanserin	
Second-generation antipsychotics: Clozapine	**Lowest propensity for EPS**

Summary of Current Treatment Guidelines for Prophylactic Use of Anticholinergic Medications[9,10,16-18]

Current treatment guidelines describe the following factors that should be considered in decisions regarding the prophylactic use of anticholinergic medications in acute-phase treatment:

- Propensity of the antipsychotic medication to cause EPS
- Patient preferences
- Patient's prior history of EPS
- Other risk factors for EPS (especially dystonia)
- Risk factors for and potential consequences of anticholinergic side effects

Use of Anticholinergic Medications in the Medi-Cal Population
A retrospective cohort study was conducted to evaluate the use of anticholinergic medications in the Medi-Cal population. All paid pharmacy claims for benztropine and trihexyphenidyl for dates of service from January 1, 2018, through December 31, 2018, were reviewed. Beneficiaries were then evaluated for concomitant use of antipsychotic medications during the same measurement year. Data were then stratified by concomitant use of first- or second-generation antipsychotics, with additional analyses conducted by individual antipsychotic medication. Descriptive statistics were used to summarize data into tables. Data analyses were performed using IBM® SPSS®, version 26.0 (Chicago, IL).

Results
Across all age groups, there were 31,118 unique beneficiaries identified with a paid claim for benztropine and/or trihexyphenidyl that has a days' supply greater than or equal to 30 days during the one-year measurement period. The majority of these beneficiaries (n = 29,006; 93%) had a paid claim for benztropine and 375 beneficiaries (1%) had at least one paid claim for both benztropine and trihexyphenidyl at distinct time periods (non-concomitant). To determine if anticholinergic use was primarily short-term, the total number of paid claims with a days' supply greater than or equal to 30 days was calculated for each beneficiary during the same one-year period (Table 2). More than half of the study population (52%) had at least six paid claims for an anticholinergic medication during the measurement year, suggesting long-term use during at least six months of the year, and 17% had paid claims greater than or equal to a one-year supply.

Table 2. Anticholinergic Use Among Medi-Cal Beneficiaries from January 1, 2018, through December 31, 2018

Number of paid claims for an anticholinergic medication ≥30 days' supply during measurement year	Utilizing Beneficiaries n (%)
≥12	5,216 (17%)
6 – 11	10,776 (35%)
2 – 5	9,395 (30%)
1	5,731 (18%)
TOTAL	**31,118 (100%)**

Among those beneficiaries with at least one paid claim for an anticholinergic medication, a total of 529 beneficiaries (2%) were 65 years of age or older, with 217 of these beneficiaries having at least six paid claims for an anticholinergic medication during the measurement year. As stated previously, the risk of adverse events related to anticholinergic medication use is increased in this population, and both benztropine and trihexyphenidyl appear on the American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults reference tool.[8] Among beneficiaries younger than 65 years of age (n = 30,630), approximately half (51%) of beneficiaries had at least six paid claims for an anticholinergic medication during the measurement year, suggesting the rate of chronic use of anticholinergic medications was higher among older adults during this time period.

An additional evaluation was conducted to determine if anticholinergic use was linked to the propensity for antipsychotic-induced EPS. Pharmacy claims data for all Medi-Cal beneficiaries were reviewed for concomitant use of antipsychotics and anticholinergics. Among those beneficiaries with a paid claim for an anticholinergic medication with greater than or equal to a 30-day supply, a total of 29,807 (96%) beneficiaries also had at least one paid claim for an antipsychotic medication during the same time period. Because of the differences in clinical recommendations for anticholinergic use, the claims data were stratified by first- and second-generation antipsychotics.

Table 3. Concomitant Anticholinergic Medication Use in Medi-Cal Beneficiaries With a Paid Claim for an Antipsychotic Medication Between January 1, 2018, and December 31, 2018*

Category	Total Utilizing Beneficiaries	Percent of Utilizing Beneficiaries with Concomitant Anticholinergic Use		
		No Use (0 paid claims)	Low Use (<6 paid claims)	High Use (≥6 paid claims)
First-Generation Antipsychotic Medications	CHLORPROMAZINE (n = 3,946)	74%	11%	15%
	FLUPHENAZINE (n = 1,692)	48%	22%	30%
	HALOPERIDOL (n = 15,208)	52%	22%	26%
	LOXAPINE (n = 630)	65%	14%	21%
	PERPHENAZINE (n = 1,932)	69%	13%	17%
	PIMOZIDE (n = 78)	92%	5%	3%
	THIORIDAZINE (n = 303)	81%	8%	11%
	THIOTHIXENE (n = 405)	47%	16%	37%
	TRIFLUOPERAZINE (n = 436)	54%	15%	31%
	ANY (n = 23,191)	58%	19%	23%
Second-Generation Antipsychotic Medications	ARIPIPRAZOLE (n = 75,087)	91%	5%	4%
	ASENAPINE (n = 2,692)	81%	9%	10%
	BREXPIPRAZOLE (n = 2,497)	89%	5%	6%
	CARIPRAZINE (n = 1,820)	83%	8%	9%
	CLOZAPINE (n = 4,246)	71%	15%	14%
	ILOPERIDONE (n = 779)	72%	8%	19%
	LURASIDONE (n = 29,649)	88%	7%	5%
	OLANZAPINE (n = 51,384)	86%	7%	7%
	PALIPERIDONE (n = 12,725)	71%	14%	15%
	QUETIAPINE (n = 86,264)	92%	4%	4%
	RISPERIDONE (n = 54,045)	82%	9%	9%
	ZIPRASIDONE (n = 9,686)	85%	7%	8%
	ANY (n = 260,655)	90%	5%	5%
	TOTAL (n = 268,245)	**89%**	**5%**	**6%**

* Beneficiaries with paid claims for more than one antipsychotic medication were included in the cohort for each antipsychotic medication in order to calculate concomitant rates of anticholinergic use for each antipsychotic medication.

As shown in Table 3, the rate of concomitant use of anticholinergics is higher among utilizing beneficiaries with a paid claim for a first-generation antipsychotic medication (42%) than among utilizing beneficiaries with a paid claim for a second-generation antipsychotic medication (10%). Concomitant anticholinergic use with second-generation antipsychotics did not seem to be correlated with EPS propensity; however, as anticholinergic use among beneficiaries with a paid claim for a higher-propensity second-generation antipsychotic like paliperidone was the same (29%) as use for beneficiaries with a paid claim for clozapine, which is thought to have the lowest propensity for EPS.

Of note, there were 4,399 beneficiaries age 65 years or older with a paid claim for an antipsychotic medication, with 11% (n = 488) having concomitant use of anticholinergic medication. Concomitant use of anticholinergic medications among these older adults was observed in 38% of those with a paid claim for a first-generation antipsychotic medication and in 11% of those with a paid claim for a second-generation antipsychotic medication, which are similar rates to the overall population.

Clinical Recommendations:

- Decisions regarding the prophylactic use of anticholinergic medications to prevent EPS should be determined on a case-by-case basis, in consideration of both patient-specific and medication-specific factors.
- In general, for patients taking second-generation antipsychotics with lower propensity for EPS, prophylactic anticholinergic medications are not recommended.
- When using an anticholinergic medication to treat acute dystonia, it is important to use the lowest dose that is able to treat the dystonia and to continue the anticholinergic medication for the shortest time needed to prevent dystonia from recurring.
- For patients who have parkinsonism associated with antipsychotic therapy, it is preferable to either lower the dosage of the antipsychotic medication or switch to another antipsychotic medication before treating with a concomitant anticholinergic medication.
- Continued use of anticholinergic medications in patients with controlled symptoms should be re-evaluated every three months.
- Older patients and/or persons with high genetic risk of cognitive disorder who use anticholinergic medications are at increased risk of cognitive decline and dementia. Providers should refer to the American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults reference tool and consider discontinuation of anticholinergic medications in these populations.

References

1. Desmarais JE, Beauclair L, Margolese HC. Anticholinergics in the era of atypical antipsychotics: short-term or long-term treatment? *J Psychopharm*. 2012;26(9): 1167 – 1174.
2. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med.* 2005;353:1209 – 1223.
3. Ascher-Svanum H, Kennedy JS, Lee D, et al. The rate, pattern, and cost of use of antiparkinsonian agents among patients treated for schizophrenia in a managed care setting. *Am J Manag Care*. 2003;9:20 – 24. Available at: http://www.ajmc.com/journals/issue/2004/2004-01-vol10-n1/Jan04-1677p20-24/. Accessed: August 12, 2019.
4. Park S, Ross-Degnan D, Adams AS, et al. Effect of switching antipsychotics on antiparkinsonian medication use in schizophrenia. *Br J Psychiatry*. 2005;187:137 – 142. Available at: https://www.cambridge.org/core/services/aop-cambridge-core/content/view/425F6D38D5DD02DAC77937CF4982AFC5/S0007125000167170a.pdf/effect_of_switching_antipsychotics_on_antiparkinsonian_medication_use_in_schizophrenia.pdf. Accessed: August 12, 2019.
5. Miller DD, Caroff SN, Davis SM, et al. Extrapyramidal side-effects of antipsychotics in a randomised trial. *Br J Psychiatry*. 2008;193:279 – 288. Available at: https://www.cambridge.org/core/services/aop-cambridge-core/content/view/8F535D8E40FD0C41D3873347C56022E2/S0007125000236234a.pdf/extrapyramidal_sideeffects_of_antipsychotics_in_a_randomised_trial.pdf. Accessed: August 12, 2019.
6. Rathbone J, Soares-Weiser K. Anticholinergics for neuroleptic-induced acute akathisia. *Cochrane Database Syst Rev*. 2006 Oct 18;4.
7. Wijegunaratne H, Qazi H, Koola MM. Chronic and bedtime use of benztropine with antipsychotics: is it necessary? *Schizophr Res*. 2014;153(1 – 3):248-249.
8. 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc, 67: 674-694. doi:10.1111/jgs.15767.
9. Buchanan RW, Kreyenbuhl J, Kelly DL, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull*. 2010;36(1):71 – 93. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2800144/pdf/sbp116.pdf. Accessed: August 12, 2019.
10. Kreyenbuhl J, Buchanan RW, Dickerson FB, et al. The schizophrenia patient outcomes research team (PORT): Updated Treatment Recommendations 2009. *Schizophr Bull*. 2010;36(1):94 – 103. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2800150/pdf/sbp130.pdf. Accessed: August 12, 2019.
11. World Health Organization Heads of Centres Collaborating in WHO co-ordinated studies on biological aspects of mental illness. Prophylactic use of anticholinergics in patients on long-term neuroleptic treatment. A consensus statement. *Br J Psychiatry*. 1990;156:412.
12. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet*. 2009;373:31 – 41.
13. Divac N, Prostran M, Jakocevski I, Cerovac N. Second-generation antipsychotics and extrapyramidal adverse effects. *Biomed Res Int*. 2014. Available at: http://dx.doi.org/10.1155/2014/656370. Accessed: August 12, 2019.

14. Werner F, Covenas R. Safety of antipsychotic drugs: focus on therapeutic and adverse effects. *Expert Opin Drug Saf.* 2014;8:1031 – 42.

15. Jibson MD and Hermann M. UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2019. Available at: https://www.uptodate.com/contents/second-generation-antipsychotic-medications-pharmacology-administration-and-side-effects. Accessed: August 12, 2019.

16. Lehman AF, Lieberman JA, Dixon LB, et al. American Psychiatric Association Steering Committee on Practice Guidelines: Practice guideline for the treatment of patients with schizophrenia, 2nd ed. *Am J Psychiatry*. 2004;161(2 suppl)1 – 56. Available at: http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/schizophrenia.pdf. Accessed: August 12, 2019.

17. Dixon L, Perkins D, Calmes C. Guideline Watch: Practice Guideline for the Treatment of Patients with Schizophrenia. American Psychiatric Association Press. September 2009. Available at: http://65.246.89.24/providers/Handbook/treatment/Schizophrenia_Guideline_Watch.pdf. Accessed: August 12, 2019.

18. Stroup TS and Gray N. Management of common adverse effects of antipsychotic medications. World Psychiatry 2018;17:341–356. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6127750/pdf/WPS-17-341.pdf. Accessed: August 12, 2019.