



Clinical Review: Concomitant Use of Anticholinergics and Antipsychotics

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 frequently not reassessed and many patients remain on them for several years.
- The consensus among the medical community is that prophylaxis of EPS with anticholinergics is generally not indicated in patients receiving antipsychotics, in particular among those 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 and older.
- Among Medi-Cal beneficiaries with a paid claim for an anticholinergic medication with greater than or equal to 30 days supply, almost all beneficiaries (96%) also had at least one paid claim for an antipsychotic medication during the same time period.
- Continued use of anticholinergic medications should be re-evaluated in patients with controlled symptoms every three months.

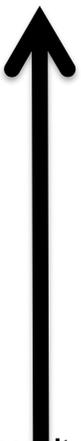
Background

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 frequently not reassessed and many patients remain on them 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 and 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^{9,10,12-14}

High potency first-generation antipsychotics: fluphenazine, haloperidol, perphenazine, pimozide, thiothixene, trifluoperazine	<p style="text-align: center;">Highest propensity for EPS</p>  <p style="text-align: center;">Lowest propensity for EPS</p>
Mid potency first-generation antipsychotics: perphenazine, loxapine Risperidone, paliperidone	
Low potency first-generation antipsychotics: chlorpromazine, thioridazine	
Olanzapine, ziprasidone, aripiprazole	
Quetiapine	
Clozapine	

Summary of Current Treatment Guidelines for Prophylactic Use of Anticholinergic Medications^{9,10,15,16}

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

1. Propensity of the antipsychotic medication to cause extrapyramidal side effects;
2. Patient preferences;
3. Patient's prior history of extrapyramidal side effects;
4. Other risk factors for extrapyramidal side effects (especially dystonia); and
5. 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 were reviewed (dates of service between September 1, 2014 and August 31, 2015). 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, and additional analyses were performed by specific antipsychotic medication.

Descriptive statistics were used to summarize data into tables. Data analyses were performed using IBM® SPSS®, version 23.0 (Chicago, IL).

Results

Across all age groups there were 34,879 unique beneficiaries identified with a paid claim for benzotropine and/or trihexyphenidyl with greater than or equal to 30 days supply during the one-year measurement period. The majority of these beneficiaries (n = 32,230; 92%) had a paid claim for benzotropine and 345 (1%) beneficiaries had at least one paid claim for benzotropine and trihexyphenidyl. To determine if anticholinergic use was primarily short-term, the total number of paid claims with greater than or equal to 30 days supply was calculated for each beneficiary (Table 2) during the same one-year period. Approximately half of the study population (51%) 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 that amounted to at least a one year supply.

Table 2. Anticholinergic Use Among Medi-Cal Beneficiaries Between September 1, 2014, and August 31, 2015

Number of paid claims for an anticholinergic medication \geq30 days supply during measurement year	n (%)
\geq 12	6,047 (17%)
6 – 11	11,707 (34%)
2 – 5	10,576 (30%)
1	6,549 (19%)
TOTAL	34,879 (100%)

Among those beneficiaries with at least one paid claim for an anticholinergic medication, a total of 360 beneficiaries (1%) were age 65 years and older, with (191 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 benzotropine and trihexyphenidyl appear on the “American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults.”⁸

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 30 days supply, a total of 35,374 (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. Of note, of the 342,539 Medi-Cal beneficiaries with a paid claim for an anti-psychotic medication during the measurement year, about one-quarter of beneficiaries (n = 87,673; 26%) had a paid claim for more than one antipsychotic medication during this time period.

Table 3. Concomitant Anticholinergic Medication Use in Medi-Cal Beneficiaries with a Paid Claim for an Antipsychotic Medication Between September 1, 2014, and August 31, 2015 *

Category	Drug Description	% Utilizing Beneficiaries with Concomitant Anticholinergic Use		
		No Use (0 paid claims)	Low Use (<6 paid claims)	High Use (≥6 paid claims)
First-Generation	CHLORPROMAZINE (n = 4,400)	72%	13%	15%
	FLUPHENAZINE (n = 2,353)	42%	20%	38%
	HALOPERIDOL (n = 17,749)	46%	26%	28%
	LOXAPINE (n = 649)	62%	13%	25%
	PERPHENAZINE (n = 2,499)	69%	15%	16%
	PIMOZIDE (n = 100)	89%	9%	2%
	THIORIDAZINE (n = 542)	82%	5%	13%
	THIOTHIXENE (n = 701)	46%	20%	34%
	TRIFLUOPERAZINE (n = 641)	51%	17%	32%
Second-Generation	ARIPIPRAZOLE (n = 73,591)	90%	6%	4%
	ASENAPINE (n = 4,051)	81%	10%	9%
	CLOZAPINE (n = 3,621)	68%	11%	21%
	ILOPERIDONE (n = 1,601)	77%	9%	14%
	LURASIDONE (n = 23,510)	85%	9%	6%
	OLANZAPINE (n = 41,244)	83%	9%	8%
	PALIPERIDONE (n = 8,722)	65%	18%	17%
	QUETIAPINE (n = 81,030)	91%	5%	4%
	RISPERIDONE (n = 62,814)	80%	10%	10%
	ZIPRASIDONE (n = 12,721)	81%	9%	10%
	TOTAL (n = 342,539)	82%	9%	9%

* 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 highest among first-generation antipsychotic medications, as expected. However, in the study population clozapine had the highest rate of chronic use of anticholinergic medications (21%) among all second-generation antipsychotics even though it is generally thought to have the lowest propensity for EPS.

Clinical Recommendations

- For patients taking first-generation antipsychotics, prophylactic use of anticholinergic medications to prevent extrapyramidal symptoms should be determined on a case-by-case basis. Patient-specific and medication-specific factors should be considered.
- For patients taking second-generation antipsychotics, prophylactic anticholinergic medications are not recommended.
- Continued use of anticholinergic medications should be re-evaluated in patients with controlled symptoms 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 consider discontinuation of anticholinergic medications in these populations.

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