Real-World Benztropine Use in DRBA-Induced Movement Disorders
DRBA-Induced Movement Disorders

• Dopamine Receptor Blocking Agent (DRBA)-induced movement disorders are movement disorders associated with the use of certain medications, such as antipsychotics.

• Movements can include:
  • Acute dystonia
  • Acute akathisia
  • Tardive dystonia
  • Tardive dyskinesia (TD)
  • Drug-induced parkinsonism

• TD is a persistent and potentially disabling movement disorder associated with prolonged exposure to DRBAs.
  • TD is often underdiagnosed due to overlap between DRBA-induced movement disorders, historic categorization of TD as extrapyramidal symptoms (EPS), and limited awareness of the number of drugs that can cause TD.

DRBAs can include:

• First-generation antipsychotics
• Second-generation antipsychotics
• Gastrointestinal medications, such as metoclopramide

DRBA, dopamine receptor blocking agent; TD, tardive dyskinesia.

Benztropine in Guidelines

- Benztropine is a medication with anticholinergic properties FDA-approved as adjunct therapy for all forms of Parkinsonism and the control of extrapyramidal disorders* (except tardive dyskinesia) due to neuroleptic drugs
- Use of multiple treatment options may be necessary in patients with multiple DRBA-induced movement disorders

American Academy of Neurology (AAN)

2013 AAN Evidence-Based Guidelines:
- No controlled trials examining the efficacy of benztropine, biperiden, chlorprothixene, and trihexyphenidyl in treating TD
- Insufficient data to determine the effectiveness of anticholinergics for the treatment of TD (Level U)

American Psychiatric Association (APA)

2022 APA DSM-5-TR: Medication Induced Movement Disorders:
- The symptoms of tardive dyskinesia tend to be worsened by stimulants, antipsychotic medication withdrawal, and anticholinergic medications (such as benztropine, commonly used to manage medication-induced parkinsonism) and may be transiently worsened by emotional arousal, stress, and distraction during voluntary movements in unaffected parts of the body

Not recommended for the treatment of TD

Benztropine Prescribing Information States:

“TD may appear in some patients on long-term therapy with phenothiazines\textsuperscript{a} and related agents, or may occur after therapy when these drugs have been discontinued”

“In treating acute drug-induced extrapyramidal disorders, after one or two weeks the drug should be withdrawn to determine continued need for it”

“Antiparkinsonism agents\textsuperscript{b} do not alleviate the symptoms of TD and in some instances may aggravate them”

“Benztropine is not recommended for use in patients with TD”

\textsuperscript{a}Examples of phenothiazines include fluphenazine, chlorpromazine, and perphenazine (all first-generation antipsychotics).
\textsuperscript{b}Refers to anticholinergics such as benztropine or trihexyphenidyl.

Beers Criteria

Benztropine (oral) and trihexyphenidyl are not recommended in older adults for prevention or treatment of extrapyramidal symptoms associated with antipsychotics according to the AGS Beers Criteria®.

What are the AGS Beers Criteria?

Explicit list of potentially inappropriate medications that are best avoided by older adults in most circumstances/specific situations, including certain diseases or conditions

Adults aged ≥65 years in all ambulatory, acute, and institutionalized settings of care, except for the hospice and palliative care settings

What is the Purpose of the AGS Beers Criteria?

Improve medication selection
Educate clinicians and patients
Reduce adverse drug events
Serve as a tool for evaluating quality of care, cost, and patterns of drug use of older adults

AGS, American Geriatric Society.
Anticholinergic Burden

• The Anticholinergic Cognitive Burden (ACB) scale is a clinical tool that identifies the severity of negative anticholinergic effects on cognition1-3
  - There are several different ACB scales cited in the literature
  - Benztropine is listed in the strongest/highest anticholinergic burden category

• A medication with the highest ACB score in healthy, older adults is associated with cognitive dysfunction and a 50% increase in risk for developing dementia4
• High anticholinergic burden in the elderly is associated with increases in5
  - Delirium
  - Falls
  - Functional and cognitive deficits

Real-World Treatment Patterns in Patients Prescribed Benztropine

A Claims Analysis From 2017-2020
A real-world, retrospective claims analysis was conducted among patients receiving an antipsychotic and newly initiating benztropine in the US to:

- Describe patient characteristics and evaluate benztropine treatment patterns

Adult patients ≥18 years were included if they had ≥1 pharmacy claim for an antipsychotic and no use of benztropine before the index date.

**Selection Window**

- Index Date: First pharmacy claim for benztropine
- 01 July 2016
- 31 March 2020
- 6 months pre-index period
- 12 months post-index period

**Study period**

- Started on 01 July 2016
- Ended on 31 March 2021

US, United States.
Chepke C. et al. NEI 2022, Colorado Springs, CO.
Claims Analysis: Patient Characteristics

Of 112,542 patients included in the analysis:

- **59%** female
- **Mean age, 46 years**
- **54%** had ≥2 comorbid conditions

Baseline comorbidities occurring in >10% of the population (N=112,542):

- Bipolar disorder: 28.3%
- Schizophrenia and affective disorders: 28.3%
- Depression: 26.3%
- Hypertension: 24.1%
- Anxiety: 24.1%
- Substance abuse: 16.2%
- Hyperlipidemia: 15.5%
- Diabetes: 15.2%
- Emotional or neurological disorders: 13.8%
- Obesity: 11.3%
Claims Analysis: Polypharmacy and Anticholinergic Burden

Medication use and anticholinergic burden in post-index period (N=112,542)

- 59.1% of patients experienced polypharmacy with claims for ≥10 medications
- 87.9% were receiving ≥1 medication with anticholinergic properties at baseline

*Mild, moderate, and severe categories adapted from acbcalc.com accessed June 2021. Mild includes “minimal” and “mild” anticholinergic burden medications from acbcalc.com.
Chepke C. et al. NEI 2022, Colorado Springs, CO.
Claims Analysis: Benztropine Utilization

Median of 5 prescription fills for benztropine over 12 months (N=112,542)

Median time to discontinuation 85 days

Benztropine Utilization (N=112,542)

- Up to 3 months: 44.3%
- >3 to 6 months: 17.4%
- >6 to 12 months: 25.6%
- >12 to 24 months: 12.7%

Data on File (VBZ-TD-0017). Neurocrine Biosciences, Inc.
Findings of polypharmacy, high anticholinergic burden, and long duration of benztropine use in this analysis demonstrates the need for appropriate evaluation and use of anticholinergics.

54% had ≥2 comorbid conditions
Most common:
- Bipolar disorder
- Schizophrenia
- Depression

Polypharmacy and anticholinergic burden were frequent
- Average 5 refills for benztropine
- 61.7% used benztropine up to 6 months before discontinuing
Healthcare Provider Perspective of Benztropine Use in Drug-Induced Movement Disorders, Including Tardive Dyskinesia

A Real-World Healthcare Provider Survey (2021-2022)
HCP Survey of Benztropine Use in DIMD

An HCP survey was conducted from December 2021 to January 2022 to understand the management of patients who present with benztropine as part of their medication regimen.

The survey consisted of the following HCPs* (N=349):

**Psychiatry**
- 151 physicians
- 98 NP/PAs

**Primary Care**
- 75 physicians
- 25 NP/PAs

Most common diagnoses in patients with a DIMD included:

- **Tremor**: 25%
- **TD**: 24%
- **Akathisia**: 21%

DIMD, Drug-induced movement disorders; HCP, healthcare provider; NP/PA, nurse practitioner/physician’s assistant; TD, tardive dyskinesia.

*HCPs were included if they treated ≥2 patients with DIMD (primary care physicians) or ≥3 patients with DIMD (psychiatric physicians and all NPs/PAs) in the past 6 months and prescribed benztropine. Each practice must have treated ≥70% adults, with ≥60% of time dedicated to direct patient interaction in outpatient or telehealth setting.

Chepke C, et al. Psych Congress 2022; New Orleans, LA.
HCP Survey: DIMD Evaluation

Frequency of DIMD Evaluation and/or Monitoring, % of Visits, Mean

<table>
<thead>
<tr>
<th>Category</th>
<th>Stable patients</th>
<th>Active medication management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psych physicians (n=151)</td>
<td>68%</td>
<td>77%</td>
</tr>
<tr>
<td>Psych NP/PAs (n=98)</td>
<td>76%</td>
<td>87%</td>
</tr>
<tr>
<td>PCP (n=75)</td>
<td>55%</td>
<td>69%</td>
</tr>
<tr>
<td>Primary care NP/PAs (n=25)</td>
<td>59%</td>
<td>69%</td>
</tr>
</tbody>
</table>

Policy in Place for Recommended Frequency for DIMD Evaluation, % of HCPs

<table>
<thead>
<tr>
<th>Category</th>
<th>Yes</th>
<th>No</th>
<th>Don’t know/Unsure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psych physicians (n=151)</td>
<td></td>
<td>33%</td>
<td>11%</td>
</tr>
<tr>
<td>Psych NP/PAs (n=98)</td>
<td></td>
<td>38%</td>
<td>12%</td>
</tr>
<tr>
<td>PCP (n=75)</td>
<td></td>
<td>56%</td>
<td>11%</td>
</tr>
<tr>
<td>Primary care NP/PAs (n=25)</td>
<td></td>
<td>77%</td>
<td>9%</td>
</tr>
</tbody>
</table>

DIMD, drug-induced movement disorder; HCP, healthcare provider; NP/PA, nurse practitioner/physician’s assistant; PCP, primary care provider.

Chepke C, et al. Psych Congress 2022; New Orleans, LA.
HCP Survey: Benztropine Initiation

Top 3 reasons to **initiate** benztropine, % of HCPs*

- **Treat non-TD DIMD**
  - Psych physicians (n=142): 90%
  - Psych NP/PAs (n=82): 87%
  - PCPs (n=71): 85%

- **Prevent non-TD DIMD**
  - Psych physicians (n=142): 92%
  - Psych NP/PAs (n=82): 84%
  - PCPs (n=71): 85%

- **Control excessive drooling**
  - Psych physicians (n=142): 45%
  - Psych NP/PAs (n=82): 24%
  - PCPs (n=71): 25%

- **Treat TD**
  - Psych physicians (n=142): 41%
  - Psych NP/PAs (n=82): 39%
  - PCPs (n=71): 36%

- **Prevent TD**
  - Psych physicians (n=142): 46%
  - Psych NP/PAs (n=82): 46%
  - PCPs (n=71): 40%

AEs, adverse events; DIMD, drug-induced movement disorder; HCP, healthcare provider; NP/PA, nurse practitioner/physician’s assistant; PCP, primary care provider; TD, tardive dyskinesia.

*When asked to rank from a list, the top 3 factors that influence initiation of benztropine. 1 indicates the option with most influence.

Chepke C, et al. Psych Congress 2022; New Orleans, LA.
HCP Survey: Benztropine Continuation and Discontinuation

Top 3 reasons to continue benztropine for >3 months, % of HCPs*

- Stable on all medications
  - Psych physicians (n=142): 75%
  - Psych NP/PAs (n=82): 65%
  - PCPs (n=71): 62%

- Prevent non-TD DIMD
  - Psych physicians (n=142): 69%
  - Psych NP/PAs (n=82): 63%
  - PCPs (n=71): 67%

- No AEs (reported or observed)
  - Psych physicians (n=142): 49%
  - Psych NP/PAs (n=82): 43%
  - PCPs (n=71): 43%

- Patient reluctance to discontinue
  - Psych physicians (n=142): 44%
  - Psych NP/PAs (n=82): 42%
  - PCPs (n=71): 42%

- Prevent TD
  - Psych physicians (n=142): 60%
  - Psych NP/PAs (n=82): 43%
  - PCPs (n=71): 29%

Benztropine Discontinuation†

- Common reasons to discontinue benztropine:
  - Comorbid conditions being exacerbated by the anticholinergic burden (65%–77%)
  - High anticholinergic burden (46%–62%)
  - <15% of all HCPs reported that their practice had a standard protocol or guidelines for discontinuing benztropine

AEs, adverse events; DIMD, drug-induced movement disorder; HCP, healthcare provider; NP/PA, nurse practitioner/physician's assistant; PCP, primary care provider; TD, tardive dyskinesia.

*When asked to rank from a list, the top 3 factors that influence the decision to continue benztropine in patients who have been taking benztropine for more than 3 months. 1 indicates the option with the most influence. †When asked to rank from a list, the top 3 factors that influence discontinuation of benztropine. 1 indicates the option with most influence.
HCP Survey: Benztropine Use and Patient Characteristics

>50% of primary care HCPs responded they would use benztropine in patients with any of the following characteristics*:

*When asked about specific patient characteristics and the use of benztropine. Five-point scale from “extremely unlikely” to “extremely likely”.

DIMD, drug-induced movement disorder; HCP, healthcare provider; NP/PA, nurse practitioner/physician’s assistant; PCP, primary care provider; TD, tardive dyskinesia.

Chepke C, et al. Psych Congress 2022; New Orleans, LA.
HCP Survey: Policies

For all HCPs, <40% had policies at their workplace to guide the frequency of evaluating patients for DIMD

More psychiatric HCPs reported these policies were present compared to primary care HCPs

<15% of all HCPs reported their practice had a standard protocol or guidelines for discontinuing benztropine

DIMD, drug-induced movement disorder; HCP, healthcare provider; NP/PA, nurse practitioner/physician’s assistant; PCP, primary care provider.
Chepke C, et al. Psych Congress 2022; New Orleans, LA.
HCP Survey: Use of Guidelines

Familiarity with the 2020 APA guidelines for the treatment of schizophrenia was low

<40% indicated familiarity when prompted

39% of psychiatric HCPs were “somewhat” or “very” familiar with the recommendations

29% of primary care HCPs

80% of those agreed that following the guidelines led to optimal treatment of DIMDs

HCPs were interested in learning more about several topics related to DIMD:

- Rationale for discontinuing benztropine: 30%
- Guidance on dose tapering of medications with anticholinergic properties: 44%
- Differential diagnosis of DIMD via telehealth: 53%

APA, American Psychiatric Association; DIMD, drug-induced movement disorder; HCP, healthcare provider.
Chepke C, et al. Psych Congress 2022; New Orleans, LA.
HCP Survey Summary

Results indicate benztropine is often used appropriately for DIMDs, but long-term use or use for the treatment of TD counter to label recommendations, and the lack of policies to evaluate and monitor DIMDs may necessitate additional education on appropriate benztropine use.

Most psychiatric visits included evaluation/monitoring for DIMD
Which was significantly higher compared to primary care visits

Main reasons to adjust benztropine therapy:

Initiate or continue > 3 months: Prevention and treatment of non-TD DIMD
Discontinue: comorbid conditions exacerbated by anticholinergic burden

>50% of Primary Care HCPs
Would use benztropine in patients
- With TD
- Aged ≥65 years
- Cognitive decline
- Anticholinergic use
- History of falls

<40% of all HCPs had policies at their workplace to guide the frequency of evaluating patients for DIMD
But 80% of those agreed that following guidelines led to optimal treatment of DIMDs

APA, American Psychiatric Association; DIMD, drug-induced movement disorder; HCP, healthcare provider; TD, tardive dyskinesia.
Chepke C, et al. Psych Congress 2022; New Orleans, LA.