DIFFERENTIAL DIAGNOSIS AND TREATMENT OF ANTIPSYCHOTIC-RELATED MOVEMENT DISORDERS
Learning Objectives

• Apply evidence-based tools and strategies for the early identification and diagnosis of patients with tardive dyskinesia, akathisia, and other movement disorders

• Formulate appropriate, individualized treatment regimens for patients with tardive dyskinesia, akathisia, and other movement disorders associated with antipsychotic use
Extra-pyramidal Symptoms (EPS)
Movement Disorders: Akathisia
Akathisia: Subjective Symptoms

- Often extraordinarily difficult for the patient to describe, to some extent because there are few subjective states to which it can be compared.
- Patients often use terms such as "anxiety" or "itching," although these do not really capture the essence of the condition.
- Since many clinicians have never experienced it, there is often a lack of common ground in communicating the problem.
Akathisia: Characteristic Distribution
Akathisia: Objective Signs

- Objective sign is disordered movement
- Mild to moderate
  - Predominantly lower extremities, usually from hips to ankles
  - Shifting positions while standing or moving the feet around while sitting
- Increasing severity
  - Can involve the entire body
  - Nearly incessant writhing and rocking, accompanied by jumping around, running, and occasionally jumping out of a chair or a bed
- Isolated reports of akathisia occurring primarily in other body regions (such as suboccipital muscles) or in strange distributions, as in hemi-akathisia (affecting only one side of the body)
- Strange or unusual distributions of either subjective or objective components: consider another process influencing the clinical presentation, such as an infarction or an abscess
Dopaminergic Hypoactivity Causes Akathisia—Or Does It?

• Suggests direct DA link
• Occurrence in Parkinson’s disease
• Similar disorders—RLS and PLMD—are treated with DA agonists
• Most APs are potent antagonists at the D2 receptor

• Suggests it’s more complicated than that
• No established direct link between parkinsonism and akathisia
• Agents that cause least EPS can still cause akathisia
• SSRIs can cause akathisia
  • Indirect stimulation of 5HT2A inhibits DA release
Antidepressant-Induced Akathisia

• There is growing awareness that akathisia can occur during treatment with antidepressants
• SSRIs have received the most reports of an association with akathisia
• TCAs and MAOIs have received fewer such reports
Hypothesized Mechanism of Akathisia: The Role of the Nucleus Accumbens


# Akathisia: Incident Rates Across Indications in FDA Registration Trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Incident Rates of Akathisia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>10-13% monotherapy; 19-25% with lithium, divalproex, or antidepressants</td>
</tr>
<tr>
<td>Asenapine</td>
<td>4-11%</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>4-14% (MDD, dosed 1-3 mg/day); 4-7% (SZ, dosed 1-4 mg/day)</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>9-14% (SZ); 20% (3-6 mg/day) or 21% (9-12 mg/day) (BP-mania)</td>
</tr>
<tr>
<td>Clozapine</td>
<td>3%</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>1-2%</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>6-22% (SZ); 4-11% (BP-depression)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>3%</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>6-9%</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1-4%</td>
</tr>
<tr>
<td>Risperidone</td>
<td>5-9%</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>8-10%</td>
</tr>
</tbody>
</table>

BP: bipolar depression. MDD: major depressive disorder. SZ: schizophrenia.
Goldberg, Ernst. Managing the side effects of psychotropic medications. 2012.
Treatment Strategies for Akathisia

- Dosage reductions
- Change to lower-risk agents if feasible
- Withdrawal akathisia can occur; allow at least 6 weeks before judging effectiveness of dose reduction/medication switch

- Benzodiazepines
- Centrally-acting beta blockers
  - Propranolol 30-90 mg/day
  - Betaxolol 10-20 mg/day
- Amantadine 100-200 mg bid
- Gabapentin 1200 mg/day
- Trazodone 100 mg/day
- Mirtazapine 15 mg/day

- Anticholinergics (e.g., benztropine): no clear value

Movement Disorders: Tardive Dyskinesia
What is dyskinesia?

- **Dyskinesia**
  - Hyperkinetic movement disorder
  - Abnormal involuntary movements
    - Nonrhythmic
      - Rapid (Suppressible)
        - Tics
      - Non-suppressible
        - Chorea; Myoclonus
      - Sustained
        - Dystonia
      - Slow
        - Athetosis
    - Rhythmic
      - Tremors

Vijayakumar D, Jankovic J. Drugs 2016;76(7):779-87;
Types of Dyskinesia

Drug-induced

• Levodopa-induced dyskinesia
• Antipsychotic-induced dyskinesia
• Dopamine receptor-blocking agents (DRBAs)

Vijayakumar D, Jankovic J. Drugs 2016;76(7):759-77; Vijayakumar D, Jankovic J. Drugs 2016;76(7):779-87.
What is tardive dyskinesia?

• Involuntary **choreoathetoid** movements usually associated with lower facial and distal extremity musculature (truncal movements also possible)
  - **Chorea**: Quick, irregular, non-stereotyped movements
  - **Athetosis**: Slow, writhing, serpentine movements

• Not associated with direct sensory problems

• Of considerable clinical, medical, and legal concern because of potential persistence despite drug discontinuation
Dopamine supersensitivity?

Blockade of D2 receptors in the nigrostriatal dopamine pathway causes them to upregulate. This upregulation may lead to tardive dyskinesia.

May contribute, but has lots of problems

Probably a better model for withdrawal-emergent dyskinesia

Other Mechanism(s) of Drug-Induced TD

- **Abnormal synaptic plasticity**
  - Chronic blockade of D2 receptors provokes maladaptive plasticity in corticostriatal transmission

- **Aberrant spine formation**
  - D2 receptors on necks; glutamate receptors on heads

- **Neuronal degeneration hypothesis**
  - Oxidative and/or excitotoxic damage from free radicals
  - Considerable basic scientific evidence
  - May offer avenues for clinical treatment

Tardive Dyskinesia: Delayed Onset

Tardive dyskinesia can occur in patients...

- After 3 months of cumulative exposure to DRBAs
- After 1 month of withdrawal of oral agent
- After 1 month of cumulative exposure in older patients
- During exposure to DRBAs
- After 2 months of withdrawal of depot agent

Symptoms should persist for longer than a month

Vijayakumar D, Jankovic J. Drugs 2016;76(7):779-87.
### Diagnostic Criteria for TD

<table>
<thead>
<tr>
<th>Source</th>
<th>Exposure</th>
<th>Severity threshold</th>
<th>Duration</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schooler-Kane (1982)</td>
<td>≥3 months</td>
<td>AIMS items: ≥3 in one area or ≥2 in 2 areas</td>
<td>Persistent ≥3 months</td>
<td>Dx of exclusion</td>
</tr>
<tr>
<td>Glazer et al. (1993)</td>
<td>≥3 months</td>
<td>AIMS items: ≥3 total with at least one ≥2 in 1 area</td>
<td>Persistent ≥2 exams</td>
<td>Dx of exclusion</td>
</tr>
<tr>
<td>DSM-IV (1994) 333.82</td>
<td>≥3 months</td>
<td>Involuntary movements</td>
<td>≥4 weeks</td>
<td>Dx of exclusion</td>
</tr>
<tr>
<td></td>
<td>≥1 month if ≥60 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSM-5 (2013) 333.85 (G24.01)</td>
<td>At least few months</td>
<td>Involuntary movements</td>
<td>≥8 weeks</td>
<td></td>
</tr>
</tbody>
</table>

DSM = *Diagnostic and Statistical Manual of Mental Disorders*; Dx = diagnosis; APA = American Psychiatric Association

Tardive Dyskinesia Prevalence in Second-Generation Antipsychotic Use

- TD prevalence is higher in patients treated with first-generation antipsychotics (FGAs)
- Recent meta-analysis comparison of TD prevalence in FGAs versus second-generation antipsychotics (SGAs) users
  - However, SGAs still show risk of TD
    - 1/5 of patients treated with SGAs showed this “rare” side effect
- In four studies, 7.2% prevalence with SGA reported in patients without prior FGA treatment

Epidemiology of Tardive Dyskinesia

Approximately 20–50% of patients receiving antipsychotics develop TD

**Risk Factors**

- Duration or cumulative antipsychotic exposure
- Potency of antipsychotic
- Older age is consistently found to be a risk factor for TD
  - **Geriatric patients**: increased movement disorders, even in neuroleptic-naïve patients
    - TD rates of 26–31% after 1 year of exposure to FGA
    - TD rates of 2.5% after 1 year of exposure to atypical antipsychotic (risperidone, quetiapine)
- Children: higher TD rates in patients taking haloperidol

Tardive Dyskinesia: Other Risk Factors

- Early onset of psychosis
- Presence of mood disorder
- Acute EPS/akathisia
- Treatment with **anticholinergics**
- Negative symptoms, cognitive symptoms
- Comorbid substance abuse
- Sex: female, especially post-menopausal
- Ethnicity?
- Genetics tendency
- 5% of medication-naïve schizophrenia patients exhibit spontaneous movements

Abnormal Involuntary Movement Scale (AIMS)
12-Item Clinician-Rated Scale to Assess Severity of Dyskinesias

• Regardless of DRBA choice and symptomatic profile, regular TD screening using the AIMS should be implemented routinely
• With FGA, examine for TD at least every 6 months
• With second-generation antipsychotics SGA, examine for TD every 12 months
• Patients at high risk of EPS:
  • examine for TD every 3 months with FGA
  • examine for TD every 6 months with SGA

Expected Course of Tardive Dyskinesia

- Long-term studies of the course of TD provide a wide range of remission rates (0–73%)\(^1-^4\)
  - Most report remission rates below 25%
- After discontinuation of the causing DRBAs, the rate of remission is low
  - Even with atypical antipsychotics, reversibility rates remain as low as only 20.5\(^%\)^5

Vinuela A et al. Tremor Other Hyperkinet Mov (N Y). 2014;4:282;
Is tardive dyskinesia preventable?

• Inform patients of risk of developing TD before initiating treatment

• Use agents with less risk of TD
  − Risk increases with potency of D2 binding

• Patients should be monitored periodically for the development of TD

• Early recognition
  − Systematic evaluation including rating scales

Vesicular Monoamine Transporter (VMAT)

• Protein integrated into the membrane of synaptic vesicles of presynaptic neurons

• Transports monoamine neurotransmitters (DA, 5HT, NE, epinephrine, histamine) into vesicles

• Two forms: VMAT1 and VMAT2
  - VMAT1: expressed mainly in peripheral nervous system
  - VMAT2: expressed mainly in monoaminergic cells of the CNS

Kenney C, Jankovic J. Expert Rev Neurother 2006;6(1):7-17;
Shen V et al. Tremor Other Hyperkinetic Movements 2013;3. doi:10.7916/D8BK1B2D;
VMAT2 Inhibition in Tardive Dyskinesia
Tetrabenazine: Efficacy and Safety

• TBZ has been shown to reduce TD symptoms by 54% \(^1\)
  
  – Approved in US in 2008 for Huntington's disease

• Studies have shown improvement of symptoms in 70–71% of patients treated with TBZ \(^2,3\)

• Level C recommendation from American Academy of Neurology 2013 (AAN Guidelines)\(^4,6\)

• Common side effects associated with TBZ include:\(^5\)
  
  – Drowsiness
  – Parkinsonism
  – Akathisia
  – Depression

# Tetrabenazine Historical Approval

<table>
<thead>
<tr>
<th>Country</th>
<th>Condition</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>Huntington’s chorea</td>
<td>2008</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Huntington’s chorea</td>
<td>2007</td>
</tr>
<tr>
<td>Germany</td>
<td>Huntington’s chorea and tardive dyskinesia</td>
<td>2007</td>
</tr>
<tr>
<td>Italy</td>
<td>Organic movement disorder and tardive dyskinesia</td>
<td>2007</td>
</tr>
<tr>
<td>France</td>
<td>Huntington’s chorea and hemiballismus</td>
<td>2005</td>
</tr>
<tr>
<td>Israel</td>
<td>Organic movement disorder and tardive dyskinesia</td>
<td>2005</td>
</tr>
<tr>
<td>Portugal</td>
<td>Organic movement disorder and tardive dyskinesia</td>
<td>2003</td>
</tr>
<tr>
<td>Canada</td>
<td>Organic movement disorder and tardive dyskinesia</td>
<td>1995</td>
</tr>
<tr>
<td>Denmark</td>
<td>Hyperkinesias</td>
<td>1980</td>
</tr>
<tr>
<td>Australia</td>
<td>Organic movement disorder and tardive dyskinesia</td>
<td>1979</td>
</tr>
<tr>
<td>New Zealand</td>
<td>Organic movement disorder and tardive dyskinesia</td>
<td>1973</td>
</tr>
<tr>
<td>Ireland</td>
<td>Organic movement disorder (tardive refused)</td>
<td>1971</td>
</tr>
<tr>
<td>UK</td>
<td>Organic movement disorder and tardive dyskinesia</td>
<td>1971</td>
</tr>
</tbody>
</table>
Metabolism of Tetrabenazine

Tetrabenazine (−)-1

Rapidly converted to dihydrotetrabenazine α, β enantiomers in a ratio of 1:1

Metabolites are metabolized via CYP2D6

Requires mandatory CYP2D6 genotyping for doses >50 mg/day

Evidence Suggests That Binding of the TBZ Metabolites to VMAT2 is Stereospecific

TBZ Enantiomers (±)-1

TBZ: tetrabenazine
DHTZB: dihydrotetrabenazine

Highest binding affinity for VMAT2

(+) - α-DHTBZ

(2R,3R,11bR)-DHTBZ (+)-2

Ki: 3.96

(+) - β-DHTBZ

(2S,3S,11bS)-DHTBZ (+)-3

Ki: 13.4

(−) - β-DHTBZ

(2R,3S,11bR)-DHTBZ (−)-3

Ki: 2,460

DHTBZ metabolites

(−) - α-DHTBZ

(2S,3S,11bS)-DHTBZ (−)-2

Ki: 23,700

Valbenazine

- Designed to deliver metabolite in a controlled fashion

\[
\begin{align*}
\text{Valbenazine} & \quad \xrightarrow{\text{metabolism}} \quad (+)-\alpha\text{-DHTBZ}
\end{align*}
\]

- Limited off-target receptor binding
- FDA approved for the treatment of TD, April 2017
  - Initial dose 40 mg/day, after 1 week increase dose to 80 mg/day
  - No need for CYP2D6 genotyping

Valbenazine: Selective VMAT2 Inhibitor

Cumulative proportion of responders during 6-week, double-blind, phase II trial

Response: at least 50% improvement in AIMS placebo n=44, NBI-98854 n=45

Valbenazine Efficacy
KINECT 3 AIMS Outcomes at Week 6

Change from baseline in the severity of TD symptoms assessed by the Abnormal Involuntary Movement Scale (AIMS) through week 6

AIMS score (least squares [LS] mean change from baseline to week 6, MMRM):
- Valbenazine 40 mg: -1.9 vs. -0.1 placebo; \(p<0.05\); effect size, \(d=0.52\)
- Valbenazine 80 mg: -3.2 vs. -0.1 placebo; \(p<0.001\); effect size, \(d=0.90\)

Valbenazine Safety and Tolerability

- PK profile permits once-daily dosing
- Psychiatric status remained stable
- Improved TD regardless of the use or type of concomitant AP
- Somnolence is the most common treatment-related AE
  - Valbenazine (all doses), 10.9%; placebo, 4.2%
  - May be due to depletion of monoamines in people with higher plasma levels of valbenazine

Valbenazine Appears Safe and Well-Tolerated Long-Term

• Data pooled from three long-term studies with valbenazine (up to 48 weeks) in adults with TD

• 66.5% of patients experienced treatment-emergent adverse events (TEAEs), but only about 14.7% discontinued the drug due to AEs

• Patients with schizophrenia:
  - urinary tract infection (6.1%)
  - headache (5.8%)
  - somnolence (5.2%)

• Patients with mood disorders:
  - headache (12.4%)
  - urinary tract infection (10.7%)
  - somnolence (9.1%)

Deutetrabenazine

- Deutetrabenazine is a selective VMAT2 inhibitor
- Deuteration is the replacing of hydrogen atoms with deuterium on a compound
  - No change in shape, size, charge, or target pharmacology of small molecules
  - Chemical bond C-D is 8x stronger
  - Prolongs half-life and improved PK

FDA Approved for Tardive Dyskinesia on August 30, 2017
- Initial dose 12 mg/day in two divided doses
- Titrate at weekly intervals by 6 mg/day based on reduction of tardive dyskinesia and tolerability
- Maximum recommended daily dosage of 48 mg (24 mg twice daily)
- No need to CYP2D6 genotyping

Pharmacokinetics of Deutetrabenazine

Mean plasma concentration
TOTAL alpha + beta (n=24-25)

Deutetrabenazine, 15 mg, fed
Deutetrabenazine, 15 mg, fasted
Tetrabenazine, 25 mg, fasted

Anderson et al. Poster presented at: American Psychiatric Association Annual Meeting; May 2016; Atlanta, GA.
Deutetrabenazine: Phase III Randomized ARM-TD Dose-Finding Trial

Double-blind, placebo-controlled, parallel-group study

At Week 12

**Placebo group**
(n=59)
Decrease in mean AIMS: 1.6 (SE=0.46)

**Deutetrabenazine group**
(n=58)
Decrease in mean AIMS: 3.0 (SE=0.45)

*p = 0.019

AEs: somnolence, headache

AIMS: Abnormal Involuntary Movement Scale.

Deutetrabenazine: Phase III Randomized AIM-TD Fixed-Dose Trial

At Week 12

**AIMS:** Abnormal Involuntary Movement Scale.

**Placebo group**
- mean AIMS: -1.4 points (SE=0.41)

**Deutetrabenazine 12 mg/d**
- mean AIMS: -2.1 points (SE 0.42)

**Deutetrabenazine 24 mg/d**
- mean AIMS: -3.2 points (SE 0.45)

**Deutetrabenazine 36 mg/d**
- mean AIMS: -3.3 points (SE 0.42)

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![Graph showing least-squares mean change in AIMS points over 12 weeks for different dose levels of deutetrabenazine compared to placebo.](image)

* p=0.006 for 24 mg/day and 0.032 for 36 mg/day
** p=0.003 for 24 mg/day and 0.018 for 36 mg/day
*** p=0.012 for 24 mg/day and 0.008 for 36 mg/day
**** p=0.003 for 24 mg/day and 0.001 for 36 mg/day

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Deutetrabenazine: Intention-to-Treat Analysis

Significant Reductions in Abnormal Involuntary Movements

- CGIC at week 12
- Treatment success was defined as a rating of “much improved” or “very much improved” on the CGIC
- Deutetrabenazine at doses of 24 mg/day and 36 mg/day were efficacious and well tolerated

Three Ways to Block VMAT2 With Three Benazines

1. **Tetrabenazine** – not approved in the United States

2. **Valbenazine** – FDA approved for the treatment of TD, April 2017

3. **Deutetrabenazine** – FDA approved for the treatment of TD, August 2017

- No head-to-head studies, all share the same fundamental mechanism
- Major differences are in pharmacokinetics, but differences in efficacy or safety are not yet well established
- Deutetrabenazine and valbenazine are established as effective treatments of TD (Level A)

American Academy of Neurology (AAN): Updated Recommendations for Treatment of Tardive Syndrome

<table>
<thead>
<tr>
<th>Level A</th>
<th>Level B</th>
<th>Level C</th>
<th>Level U</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>must</strong> be recommended as treatment</td>
<td><strong>should</strong> be considered as treatment</td>
<td><strong>might</strong> be considered as treatment</td>
<td>insufficient evidence to support or refute</td>
</tr>
</tbody>
</table>
| • Deutetrabenazine  
• Valbenazine | • Clonazepam  
• Ginkgo biloba | • Amantadine  
• Tetrabenazine  
• Pallidal deep brain stimulation (intractable TD) | • Withdrawing causative agents  
• Switching from typical to atypical DRBA |

Movement Disorders: Drug-Induced Parkinson’s (DIP)
Label Change for VMAT-2

- Valbenazine – section 5.3
- Deutetrabenazine – section 5.5

Ways you can see co-existence of DIP and TD

- Exposure to DRBAs (Co-existent)
- VMAT-2 Mechanism of Action
- Co-existent but unrecognized
Drug-Induced Parkinson’s (DIP)

• DIP is the most common movement disorder induced by drugs that affect dopamine receptors (e.g., DRBAs)

• Risk factors: age, female gender

• Genetic risk factors: genes associated with GABA receptor-signaling pathway are involved in neuroleptic-induced TD in schizophrenic patients

Which drugs are most commonly associated with high risk for DIP?

<table>
<thead>
<tr>
<th>Table 1. Common offending drugs of drug-induced parkinsonism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug frequently causing parkinsonism</strong></td>
</tr>
<tr>
<td>Typical antipsychotics</td>
</tr>
<tr>
<td>Phenothiazine: chlorpromazine, prochlorperazine, perphenazine, fluphenazine, promethazine</td>
</tr>
<tr>
<td>Butyrophenones: haloperidol</td>
</tr>
<tr>
<td>Diphenylbutylpiperidine: pimozide</td>
</tr>
<tr>
<td>Benzamide substitutes: sulpiride</td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
</tr>
<tr>
<td>Risperidone, olanzapine, ziprasidone, aripiprazole</td>
</tr>
<tr>
<td>Dopamine depleters</td>
</tr>
<tr>
<td>Reserpine, tetrabenazine</td>
</tr>
<tr>
<td>Antiemetics</td>
</tr>
<tr>
<td>Metoclopramide, levosulpiride, clebopride</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
</tr>
</tbody>
</table>

SSRI: selective serotonin reuptake inhibitor.
Changes to the Brain Due to Blockade of D2 Receptors by DRBAs
Dopamine Transporter Scans May Be Helpful in Diagnosing DIP
## DIP Trajectories/Outcomes

<table>
<thead>
<tr>
<th>Prognosis</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Full and long-lasting recovery from DIP with no subsequent developed parkinsonism</td>
</tr>
<tr>
<td>Type II</td>
<td>Persistence but not progression of parkinsonism</td>
</tr>
<tr>
<td>Type III</td>
<td>Persistence and eventual worsening of parkinsonism</td>
</tr>
<tr>
<td>Type IV</td>
<td>Full remission of parkinsonism but later reappearance after discontinuation of the drug</td>
</tr>
</tbody>
</table>
### Treatment for DIP

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who cannot stop taking antipsychotics for psychiatric reasons</td>
<td>Switch to atypical antipsychotics with lower risk of EPS</td>
</tr>
<tr>
<td>Patients who have been prescribed DA antagonists due to GI disturbances</td>
<td>Stop taking offending drug immediately</td>
</tr>
</tbody>
</table>

**Anticholinergics**

- Trihexyphenidyl
- Benztropine
- Amantadine
- Levodopa / Dopamine Agonists
- DBS ?

How do you manage TD patients on VMAT-2 who also have DIP?
Summary

- Differentiating among various extrapyramidal symptoms (EPS) is important for accurate diagnosis of movement disorders.
- Agents associated with the least EPS risk can still cause akathisia.
- Tardive dyskinesia (TD) remains a serious risk of APs and other DRBAs.
- Drug-induced parkinsonism (DIP) is the most common movement disorder induced by DRBAs.
- Awareness of effective treatment strategies available for akathisia, TD, and DIP enhances appropriate treatment of movement disorders.