Ants in Your Pants?
Exploring Alternative Treatment Options for Acute Antipsychotic-Induced Akathisia

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Learning Objectives

- Discuss proposed mechanisms for antipsychotic-induced akathisia (AIA)
- List risk factors for the development of akathisia secondary to antipsychotic pharmacotherapy
- Identify traditional agents utilized in the management of acute antipsychotic-induced akathisia
- Describe the rationale for the use of 5-HT_{1D} agonists and 5-HT_{2A} antagonists in the treatment of acute AIA
**What is Akathisia?**

1. Extrapyramidal Symptoms
   a. Dystonia/dyskinesia
      i. Dystonic reaction
         1. Sustained posture from continuous muscle contraction
         2. Most common in tongue, jaw, throat, neck, eyes, back, and extremities
      ii. Dyskinesia
         1. Repetitive, abnormal, involuntary jerking movements
         2. Typically involves lower face and distal extremities
   b. Pseudoparkinsonism
      i. Antipsychotic-induced parkinsonian symptoms
         1. Bradykinesia (slowed movement)
         2. Tremor (typically while at rest)
         3. Cogwheel rigidity
   c. Akathisia
      i. Subjective feeling of inner restlessness
      ii. Objective inability to sit/stand still

**Symptoms of Akathisia**

1. Subjective symptoms
   a. Impatience
   b. Irritability
   c. Panic
   d. Tension
2. Objective symptoms
   a. Rocking
   b. Crossing/uncrossing legs
   c. Fidgeting of legs
   d. Myoclonic jerks of feet
   e. Pacing
   f. Shuffling of feet
   g. Shifting weight

**Akathisia Subtypes**

<table>
<thead>
<tr>
<th>Table 1. Descriptions of Akathisia Subtypes</th>
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<tbody>
<tr>
<td><strong>Subtype</strong></td>
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<tr>
<td>-------------</td>
</tr>
<tr>
<td>Pseudoakathisia</td>
</tr>
<tr>
<td>Acute Akathisia</td>
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<tr>
<td>Chronic Akathisia</td>
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<tr>
<td>Tardive Akathisia</td>
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<tr>
<td>Withdrawal Akathisia</td>
</tr>
</tbody>
</table>
**Pathophysiology of AIA**\(^3,7-11\)

I. Imbalance between dopaminergic, and noradrenergic and serotonergic systems
   a. Dopamine (DA) blockade via norepinephrine (NE) hyperactivity
   b. Inhibition of DA release via serotonin (5-HT)-2 activity
   c. Direct blockade of D\(_2\) dopaminergic receptors

II. Other associated neurochemicals
   a. Acetylcholine (ACh)
   b. Gamma-aminobutyric acid (GABA)
   c. Neuropeptides

*Figure 1. Select Brain Regions Involved in Dopaminergic Neurotransmission*\(^{12}\)

\(a=\) nigrostriatal pathway, \(b=\) mesolimbic pathway, \(c=\) mesocortical pathway, \(d=\) tuberoinfundibular pathway, \(e=\) multi-site dopamine pathway, DLPFC=dorsolateral prefrontal cortex, VMFC=ventromedial prefrontal cortex

**Agent-Specific Risk of AIA**\(^4,8,13-19\)

I. First generation antipsychotics (FGAs): 25%

II. Second generation antipsychotics (SGAs)
   a. Lurasidone (Latuda): 15%
   b. Aripiprazole (Abilify): 9-15%
   c. Risperidone (Risperdal): 13%
   d. Ziprasidone (Geodon): 7-24%
   e. Paliperidone (Invega): 7%
   f. Asenapine (Saphris): 6%
g. Quetiapine (Seroquel): 3-10%

h. Olanzapine (Zyprexa): 3.7%

i. Clozapine (Clozaril): 3%

j. Iloperidone (Fanapt): 1%

**Risk Factors for AIA**

**Table 2. Risk Factors Associated with the Development of AIA**

<table>
<thead>
<tr>
<th>Antipsychotic-Related Risk Factors</th>
<th>Other Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose</td>
<td>Previous akathisia</td>
</tr>
<tr>
<td>High potency</td>
<td>Presence of other EPS</td>
</tr>
<tr>
<td>Rapid titration</td>
<td>Use of other psychotropics</td>
</tr>
<tr>
<td>Increased duration of use</td>
<td>Use of other causative agents</td>
</tr>
<tr>
<td>Parenteral administration</td>
<td>Affective disorders</td>
</tr>
<tr>
<td></td>
<td>Negative symptoms</td>
</tr>
<tr>
<td></td>
<td>Cognitive dysfunction</td>
</tr>
<tr>
<td></td>
<td>Substance abuse</td>
</tr>
<tr>
<td></td>
<td>Iron deficiency</td>
</tr>
</tbody>
</table>

**Figure 2. Dose-Associated Symptomatology of AIA**

**Differential Diagnoses**

I. Agitation

II. Activation

III. Anxiety

IV. Neuropsychiatric disorders

V. Neuroleptic rebound syndrome

VI. Restless leg syndrome

VII. Periodic limb movement disorder
**COMPLICATIONS OF AKATHISIA**

I. Insomnia  
II. Suicidality  
III. Maladaptive behaviors  
IV. Tardive dyskinesia  
V. Worsening psychosis  
VI. Non-compliance  
VII. Impaired treatment response

**BARNES AKATHISIA RATING SCALE (BARS)**

I. Most commonly used scale for akathisia diagnosis  
a. Established validity and high inter-rater reliability  
II. Scale components  
a. Subjective and objective subscales  
i. May be used to detect change in symptoms with treatment  
b. Global subscale  
i. Most appropriate indicator of severity in clinical/research settings  
ii. May be used to estimate incidence/prevalence

**MANAGEMENT OF AIA**

I. Prevention of AIA  
a. Initiation of lower risk antipsychotics  
b. Slow dose titration to lowest therapeutic dose  
II. Treatment of AIA  
a. Modify antipsychotic pharmacotherapy  
a. Initiate anti-akathisia agent

**RECEPTOR PHARMACOLOGY OF ANTI-AKATHISIA THERAPY**

**Table 3. Receptor Pharmacology of Supported Anti-Akathisia Therapy**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Receptor Site</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>β</em></td>
</tr>
<tr>
<td>Propranolol</td>
<td>X</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>X</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>X</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>X</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>X</td>
</tr>
<tr>
<td>Trazodone</td>
<td>X</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>X</td>
</tr>
</tbody>
</table>

*This is not an all-inclusive list, *adrenergic receptors  
H=histamine, BZD= benzodiazepine, M= muscarinic, D=dopaminergic, 5-HT=serotonergic,  
SERT=serotonin transporter, DAT=dopamine transporter, NET=norepinephrine transporter
TRADITIONAL TREATMENT OPTIONS FOR AIA \textsuperscript{3-5,8,22-24,34-37}

I. Propranolol (Inderal)
   a. Dosing
      i. Initial: 10 mg by mouth three times daily
      ii. Max: 120 mg/day
   b. Evidence for use
      i. Efficacy rates of 30-70\% reported in practice
      ii. 2004 Cochrane Review
         1. Insufficient data for management of akathisia
   c. Adverse effects
      i. Orthostasis
      ii. Bradycardia
   d. Contraindications/precautions
      i. Asthma
      ii. Cardiac conduction abnormalities

II. Benzodiazepines
    a. Agents
       i. Clonazepam (Klonopin)
          1. Dosing: 0.5-3 mg/day
       ii. Diazepam (Valium)
          1. Dosing: 5-15 mg/day
       iii. Lorazepam (Ativan)
          1. Dosing: 1-2 mg/day
    b. Evidence for use
       i. 1999 Cochrane Review
          1. May reduce AIA symptoms over a short follow-up period
       ii. Greater efficacy with clonazepam and lorazepam vs. diazepam
    c. Adverse effects
       i. Central nervous system effects
       ii. Respiratory depression
       iii. Risk of tolerance/dependence
    d. Contraindications/precautions
       i. Use cautiously in patients with hepatic insufficiency
       ii. Avoid in geriatric patients when possible

III. Anticholinergics
    a. Agents
       i. Benztropine (Cogentin)
          1. Dosing
             a. 2-8 mg/day
             b. Given daily or in 2-3 divided doses
       ii. Trihexyphenidyl (Artane)
          1. Dosing
             a. 2-10 mg/day
             b. Divided into 3-4 doses/day
    b. Evidence for use
       i. 2002 Cochrane Review
          1. Evidence for use of anticholinergics in AIA is controversial
ii. 39-73% response rate in studies
iii. Most efficacy seen in patients with concomitant parkinsonism and patients on concomitant benzodiazepine therapy

c. Adverse effects
   i. Blurred vision
   ii. Constipation
   iii. Xerostomia
   iv. Cognitive impairment
   v. Sedation
   vi. Tachycardia
   vii. Urinary retention

d. Contraindications/precautions
   i. Use cautiously in patients with tardive dyskinesia, hepatic impairment, renal impairment, benign prostatic hypertrophy, cardiovascular disease, and gastrointestinal obstruction
   ii. Avoid in patients with narrow-angle glaucoma

**Newer Alternatives for AIA**

I. 5-HT\textsubscript{2A} Antagonists
   a. Agents
      i. Cyproheptadine (Periactin)
         1. Dosing: 4 mg by mouth four times daily
         2. Evidence for use: comparable efficacy to propranolol
         3. Adverse effects
            a. Sedation
            b. Weight gain
            c. Gastrointestinal adverse effects
         4. Contraindications/precautions
            a. Contraindicated in patients who are breastfeeding, those who are on a monoamine oxidase inhibitor (MAOI), and in patients with narrow-angle glaucoma, urinary obstruction, and stenosing peptic ulcers
      ii. Mirtazapine (Remeron)
         1. Adverse effects
            a. Sedation
            b. Weight gain
            c. Constipation
         2. Contraindications/precautions
            a. Risk of affective switch when used in patients with bipolar disorder
            b. High doses associated with akathisia development
            c. Rapid titration and initiation at high doses associated with increased suicidality in youth
            d. Avoid concomitant use with MAOIs
      iii. Trazodone (Desyrel)
         1. Adverse effects
            a. Sedation
b. Orthostasis
c. Nightmares
d. Priapism

2. Contraindications/precautions
   a. Risk of affective switch when used in patients with bipolar disorder
   b. Rapid titration and initiation at high doses associated with increased suicidality in youth
   c. Avoid concomitant use with MAOIs

II. 5-HT₁D agonists
   a. Zolmitriptan (Zomig)
   b. Adverse effects
      i. Nausea
      ii. Dizziness
      iii. Paresthesia/hyperesthesia(asthenia
      iv. Sedation
      v. Cardiac adverse effects
   c. Contraindications/precautions
      i. Contraindicated in patients with significant underlying cardiovascular disease, peripheral vascular disease, history of stroke or hemiplegic or basilar migraine, and concomitant MAOI

III. Vitamin B₆ (Pyridoxine)
   a. Dosing
      i. 600 mg by mouth twice daily
   b. Mechanism of action
      i. Co-factor for decarboxylation of dopa to dopamine
      ii. Required for function of enzymes involved in serotonin, GABA, and melatonin synthesis
      iii. Possesses antioxidant properties
   c. Evidence for use
      i. Shown to be effective when compared to placebo for improvement of BARS subjective and global subscales, with a trend toward improvement in the BARS objective subscale
   d. Adverse effects
      i. Headache
      ii. Nausea
   e. Contraindications/precautions
      i. Caution should be exercised in patients with renal dysfunction, as certain intravenous formulations of pyridoxine contains aluminum
      ii. Large intravenous doses are associated with an increased risk of seizure

**Agents with Limited Efficacy in the Management of AIA**

I. Opiates
II. Clonidine (Catapres)
III. Amantadine (Symmetrel)
IV. Ropinirole (Requip)
V. Buspirone (Buspar)
### Low Dose Mirtazapine: A New Option in the Treatment of Antipsychotic-Induced Akathisia. A Randomized, Double-Blind, Placebo- and Propranolol-Controlled Trial

<table>
<thead>
<tr>
<th>Study Objective</th>
<th>To determine mirtazapine’s efficacy and tolerability in the treatment of akathisia secondary to typical antipsychotics, when compared to the current first-line treatment option for akathisia, propranolol</th>
</tr>
</thead>
</table>
| Inclusion Criteria | • Psychiatric inpatients  
• Score of ≥ 2 on the BARS  
• Diagnosis of acute AIA supported by DSM-IV criteria  |
| Exclusion Criteria | • Contraindications to beta-blockers  
• Treatment of emergent akathisia prior to screening  
• Diagnosis of non-acute akathisia  
• Treatment with long-acting antipsychotics  
• Change in AP regimen within 3 days of akathisia onset  |
| Treatment Arms | • Mirtazapine 15 mg by mouth once daily (n=30)  
• Propranolol 40 mg by mouth twice daily (n=30)  
• Placebo (n=30)  |
| Methodology | • Randomization via table of random numbers  
• Allocation using randomized block design  
• Identical capsules dispensed by study pharmacist twice daily  
• BARS conducted at baseline, day 3, and day 7  
• Simpson-Angus Scale (SAS), Brief Psychiatric Rating Scale (BPRS), and Hamilton Rating Scale for Depression (HAM-D) conducted at baseline and on day 7  
• Adverse effects assessed daily  |
Primary Outcomes
• Between-group differences in BARS global scores
• Between-group differences in proportion of responders

Secondary Outcomes
• Between-group difference in psychometric scale score change
• Between-group difference in adverse events

Statistical Analysis
• Intention to treat analysis
• 30 patients per group to achieve 90% power to detect a 40% difference in response rate between treatment and placebo at a significance level of 0.05, with a 25% attrition rate
• Analysis of between-group differences in demographic and clinical variables, and in changes in psychometric scale scores with ANOVA or Chi-Square, as appropriate

Study Population
• No statistically significant difference in baseline characteristics between groups (mostly men with schizophrenic disorders treated with haloperidol, average age=~34 years old)
• Over 20 dropouts

<table>
<thead>
<tr>
<th>Table 4. Mean Change in BARS Global Subscale</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Baseline to Day 3</td>
</tr>
<tr>
<td>Day 3 to 7</td>
</tr>
<tr>
<td>Responder Rate (%)</td>
</tr>
<tr>
<td>NNT</td>
</tr>
</tbody>
</table>

BARS=Barnes Akathisia Rating Scale, NNT=number needed to treat

- Overall reductions in the BARS subscales from baseline to day 7 were 34% in the mirtazapine group, 29% in the propranolol group, and 11% in the placebo group
- No significant difference in BARS subscales between groups
- No between-group difference for change in SAS, BPRS, HAM-D

Safety
- Higher incidence of drowsiness in the mirtazapine group (36.7%) vs. 26.6% with propranolol and 20% with placebo
- 16.7% of patients in the propranolol group prematurely discontinued the study due to hypotension/bradycardia

Strengths
- Comparison against placebo and active comparator
- Use of intention-to-treat analysis
- One trained research psychiatrist performed all rating scales
- Scales performed prior to medication administration
- Magnitude of change in BARS global scales for mirtazapine and
propranolol were similar to those seen in previous studies

- Short trial duration (7 days) and small sample size
- Failure to mention when current AP regimens initiated
- Discrepancy between number of dropouts in figure vs. text
- Focus on akathisia induced by typical antipsychotics
- Continuation of anticholinergics/BZDs initiated prior to study

Conclusions
Mirtazapine is a promising alternative to propranolol for the treatment of AIA, considering its comparable efficacy, greater tolerability, and more convenient dosing

II. Stryjer R, et al.\textsuperscript{39}

<table>
<thead>
<tr>
<th>Trazodone for the Treatment of Neuroleptic-Induced Acute Akathisia: A Placebo-Controlled, Double-Blind, Crossover Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study objective</strong></td>
</tr>
<tr>
<td>To further evaluate the efficacy of trazodone for the treatment of AIA in a controlled clinical trial</td>
</tr>
<tr>
<td><strong>Inclusion Criteria</strong></td>
</tr>
</tbody>
</table>
| • Inpatients between 18 and 60 years old
• Diagnosis of schizophrenia or schizoaffective disorder confirmed by DSM-IV criteria
• Treatment with same antipsychotic for ≥ 3 months
• Presence of akathisia, confirmed by a BARS score of ≥ 2 |
| **Exclusion Criteria** |
| • Treatment with beta-blockers, anticholinergics, or BZDs
• Presence of any unstable medical condition |
| **Treatment Arms** |
| • Trazodone 100 mg by mouth each night at bedtime on days 1-3, then placebo by mouth at bedtime on days 4-6 (n=8)
• Placebo by mouth each night at bedtime on days 1-3, then trazodone 100 mg by mouth at bedtime on days 4-6 (n=5) |
| **Methodology** |
| • Randomization to trazodone 100 mg days 1-3, then placebo days 4-6, or placebo days 1-3, then trazodone 100 mg days 4-6
• No washout period between treatments
• Trazodone and placebo administered in identical capsules
• Assessment via the BARS global subscale, SAS, HAM-D, and Positive and Negative Syndrome Scale (PANSS) for schizophrenia by a single rater at baseline and on days 3 and 6 |
| **Study Outcomes** |
| • Treatment effect
• Period effect
• Between-group differences in adverse effects |
| **Statistical Analysis** |
| • Baseline characteristics between groups compared using paired t tests
• Two-tailed paired t tests to assess treatment and period effects
• Effect size calculated via Cohen’s method
• Treatment by group interactions analyzed via 2X2 repeated measures analysis of variance models with between-subjects factor of treatment and within-subject factor of days |
Study Population

- Included 7 men and 6 women
- Mean age = 43 years old
- 9 patients with schizophrenia
- 4 patients with schizoaffective disorder
- No significant differences in outcome measures at baseline

**Table 5. Effects of Trazodone vs. Placebo**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (Mean ± Standard Deviation)</th>
<th>Trazodone (Mean ± Standard Deviation)</th>
<th>T₁₂</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>BARS Objective</td>
<td>-0.15 ± 0.69</td>
<td>-1 ± 0.71</td>
<td>2.86*</td>
<td>1.21</td>
</tr>
<tr>
<td>BARS Subjective Awareness</td>
<td>-0.15 ± 0.9</td>
<td>-1.31 ± 0.95</td>
<td>2.74*</td>
<td>1.25</td>
</tr>
<tr>
<td>BARS Subjective Distress</td>
<td>0.08 ± 0.76</td>
<td>-1 ± 0.82</td>
<td>3.74*</td>
<td>1.16</td>
</tr>
<tr>
<td>BARS Global</td>
<td>0 ± 1.08</td>
<td>-1.69 ± 1.18</td>
<td>3.39*</td>
<td>1.49</td>
</tr>
<tr>
<td>SAS</td>
<td>-1.84 ± 3.96</td>
<td>-1.54 ± 4.89</td>
<td>0.14</td>
<td>0.07</td>
</tr>
<tr>
<td>HAM-D</td>
<td>-0.23 ± 2.74</td>
<td>-1.61 ± 2.75</td>
<td>0.99</td>
<td>0.5</td>
</tr>
<tr>
<td>PANSS</td>
<td>-3.69 ± 7.65</td>
<td>-3.15 ± 8.54</td>
<td>0.14</td>
<td>0.07</td>
</tr>
</tbody>
</table>

* p<0.05, ¥ p<0.01, 2 tailed paired t tests

BARS=Barnes Akathisia Rating Scale, SAS=Simpson Angus Scale, HAM-D=Hamilton Rating Scale for depression, PANSS= Positive and Negative Syndrome Scale

- Significant treatment by day interactions (days 1-3) of the subjective ($f_{1,11}=5.39$, $p=0.04$), distress ($f_{1,11}=5.31$, $p=0.04$), and global ($f_{1,11}=8.13$, $p=0.016$) scores
- Significant treatment by day interactions (days 3-6) of distress ($f_{1,11}=6.14$, $p=0.03$), and objective ($f_{1,11}=5.31$, $p=0.04$) scores

Efficacy

Safety

- No clinically significant adverse effects in either group

Strengths

- Placebo-controlled
- Scales performed by a single rater
- Antipsychotic doses remained stable during the study period
- Validated previously conducted open-label study

Limitations

- Short trial duration (6 days)
- Small sample size
- Failure to mention when current AP regimens initiated
- Lack of a washout period
- Method of randomization not addressed
- Method of assessment for adverse effects not discussed
- Information on antipsychotic regimens not provided

Conclusions

Trazodone is an effective treatment for AIA compared to placebo
### Zolmitriptan compared to propranolol in the treatment of acute neuroleptic-induced akathisia: A comparative double-blind study

<table>
<thead>
<tr>
<th><strong>Study Objective</strong></th>
<th>To further evaluate the efficacy of zolmitriptan for the treatment of AIA in a controlled clinical trial, and in comparison to the traditional first-line treatment option for AIA, propranolol.</th>
</tr>
</thead>
</table>
| **Inclusion Criteria** | - Inpatient admission for psychotic exacerbation of schizophrenia or schizoaffective disorder  
- Diagnosis of AIA confirmed by DSM-IV-TR  
- Minimal BARS score of 5  
- Stable antipsychotic dose for ≥ 3 days prior to study initiation |
| **Exclusion Criteria** | - Age < 18 years old or > 60 years old  
- Significant, concomitant cardiovascular disease |
| **Treatment Arms** | - Zolmitriptan 2.5 mg by mouth three times daily (n=14)  
- Propranolol 40 mg by mouth three times daily (n=19) |
| **Methodology** | - Randomization via a table of random numbers  
- All patients received identical capsules for 3 consecutive days  
- Antipsychotic doses remained unchanged throughout study  
- BARS, SAS, HAM-D, HAM-A, and PANSS conducted 1 day prior to study initiation (day 0), day 3, and day 7  
- Pulse and blood pressure measured twice daily during study |
| **Study Outcomes** | - Change in BARS, HAM-D, Hamilton Rating Scale for Anxiety (HAM-A), SAS, and PANSS across groups  
- Between-group differences in pulse (HR)/blood pressure (BP) |
| **Statistical Analysis** | - Fisher’s Exact Test, General Linear Model (GLM), and unpaired and paired student’s t-test with time as the within factor and group as the between factor  
- Contrasts analysis |
| **Study Population** | - Study completed by 8 patients on zolmitriptan and 14 patients on propranolol  
- No statistically significant differences in baseline characteristics or outcome measures between groups or between completers and non-completers at baseline  
- In both groups, most patients were males and had schizophrenia, and average age was between 35-38 years old |
| **Efficacy** | - Mean BARS scores decreased significantly across both groups between days 0 and 3 (p<0.002) and increased significantly across both groups from days 3 to 7 (p<0.028)  
- A 4.07 point (39.5%) decrease was observed in the propranolol group from days 0 to 3, compared to a 3.85 point (26.1%) decrease in the zolmitriptan group  
- GLM analysis showed a significant effect for time ($F_{2,36}=9.199$, $P<0.001$); however, effects for group and the interaction between group and time were not significant  
- Significant reductions in SAS, HAM-D, HAM-A, and PANSS in each group |
**Selection of an Anti-Akathisia Agent**

### General Management of Acute AIA

#### Beta-Blocker
propranolol 40-120 mg/day

#### 5-HT2A Antagonist
- mirtazapine 15 mg/day
- trazodone 100 mg/day
- cyproheptadine 8-16 mg/day

### Continued Distress

#### Addition of or Change to Benzodiazepine
- lorazepam 1-2 mg/day
- clonazepam 0.5-3 mg/day
- diazepam 5-15 mg/day

### Treatment Failure

#### Use of Alternative Agent
- pyridoxine 1200 mg/day
- zolmitriptan 7.5 mg/day
- limited efficacy agents

### Concomitant Parkinsonism

#### Anticholinergic Monotherapy
- benztpine 2-8 mg/day
- trihexyphenidyl 2-10 mg/day

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**Figure 3. General Management of Acute AIA**
**Figure 4. Selecting a First-Line Agent for Acute AIA in Special Populations**

**SUMMARY**
I. AIA is difficult to recognize and distressing to the patient
II. Traditional treatment options for AIA have limited data supporting their efficacy
III. Newer treatment options aid clinicians in understanding AIA pathophysiology
IV. As the mechanism of AIA further unravels, more efficacious treatment options may be discovered

**REFERENCES**


APPENDIX A: RECEPTOR BINDING AFFINITIES OF ATYPICAL ANTIPSYCHOTICS

Table 6. Select Receptor Binding Affinities of Second Generation Antipsychotics (SGAs)

<table>
<thead>
<tr>
<th>SGA</th>
<th>5-HT&lt;sub&gt;2A&lt;/sub&gt;</th>
<th>D&lt;sub&gt;2&lt;/sub&gt;</th>
<th>α&lt;sub&gt;1&lt;/sub&gt;</th>
<th>H&lt;sub&gt;1&lt;/sub&gt;</th>
<th>M&lt;sub&gt;1&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lurasidone</td>
<td>0.47</td>
<td>0.99</td>
<td>10.8</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>3.4</td>
<td>0.45</td>
<td>47</td>
<td>1</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.5</td>
<td>4</td>
<td>0.7</td>
<td>20</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>0.4</td>
<td>5</td>
<td>11</td>
<td>50</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>0.25</td>
<td>4.6</td>
<td>80</td>
<td>13.6</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Asenapine</td>
<td>0.006</td>
<td>1.3</td>
<td>1.2</td>
<td>1</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>31</td>
<td>770</td>
<td>8.1</td>
<td>19</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>4</td>
<td>11</td>
<td>19</td>
<td>7</td>
<td>1.9</td>
</tr>
<tr>
<td>Clozapine</td>
<td>16</td>
<td>126</td>
<td>7</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>5.6</td>
<td>6.3</td>
<td>36</td>
<td>473</td>
<td>&gt;1000</td>
</tr>
</tbody>
</table>

*Receptor binding affinities are expressed as Ki (inhibition constant) values, with the lowest value correlating to the strongest binding affinity. Ki values may vary based on antipsychotic dose.

APPENDIX B: BARNES AKATHISIA RATING SCALE (BARS)

Instructions: Observe patient while seated, and then standing during neutral conversation (minimum of two minutes each). Symptoms observed in other situations may also be rated. Subjective phenomena should be identified via direct questioning.

<table>
<thead>
<tr>
<th>Objective Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subjective Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awareness of Restlessness</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>
### Subjective Rating
Distress Related to Restlessness

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No distress</td>
</tr>
<tr>
<td>1</td>
<td>Mild distress</td>
</tr>
<tr>
<td>2</td>
<td>Moderate distress</td>
</tr>
<tr>
<td>3</td>
<td>Severe distress</td>
</tr>
</tbody>
</table>

### Global Clinical Assessment of Akathisia

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absence of akathisia: No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia.</td>
</tr>
<tr>
<td>1</td>
<td>Questionable akathisia: Non-specific inner tension and fidgety movements.</td>
</tr>
<tr>
<td>2</td>
<td>Mild akathisia: Awareness of restlessness in the legs and/or inner restlessness worse when required to stand still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate akathisia: Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing.</td>
</tr>
<tr>
<td>4</td>
<td>Marked akathisia: Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least five minutes. The condition is obviously distressing.</td>
</tr>
<tr>
<td>5</td>
<td>Severe akathisia: The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia.</td>
</tr>
</tbody>
</table>

### Scoring the Barnes Akathisia Rating Scale (BARS)
Objective and subjective subscales may be summed to provide a total score ranging from 0 to 9. The Global Clinical Assessment of Akathisia is scored separately.

### APPENDIX C: LITERATURE ON SEROTONERGIC AGENTS FOR TREATMENT OF AIA

#### Table 7. Studies of Use of Serotonergic Agents in the Treatment of AIA

<table>
<thead>
<tr>
<th>Medication*</th>
<th>Study Design</th>
<th>Total Sample Size</th>
<th>Dose (mg/day)</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buspirone</td>
<td>Open trial</td>
<td>10</td>
<td>10-30</td>
<td>BARS, SAS</td>
<td>2 improved, 6 unchanged, 2 worsened</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>Open trial</td>
<td>17</td>
<td>16</td>
<td>HAS, BPRS, HAM-D, AIMS</td>
<td>15/17 improved (6/17 complete resolution)</td>
</tr>
<tr>
<td>Cyproheptadine vs. propranolol</td>
<td>Double blind</td>
<td>30</td>
<td>16</td>
<td>BARS, SAS, BRPS</td>
<td>40% BARS decrease w/ cyproheptadine, 42% w/ propranolol</td>
</tr>
<tr>
<td>Medication*</td>
<td>Study Design</td>
<td>Total Sample Size</td>
<td>Dose (mg/day)</td>
<td>Outcome Measures</td>
<td>Results^y</td>
</tr>
<tr>
<td>-------------</td>
<td>--------------</td>
<td>-------------------</td>
<td>---------------</td>
<td>------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Granisetron</td>
<td>Open trial</td>
<td>10</td>
<td>2</td>
<td>BARS,SAS, mLAS, BRPS, HAM-D</td>
<td>2 improved, 5 unchanged, 3 dropouts</td>
</tr>
<tr>
<td>Mianserin</td>
<td>Open trial</td>
<td>16</td>
<td>15</td>
<td>BARS,SAS</td>
<td>Improvement of all 3 BARS subscales</td>
</tr>
<tr>
<td>Mianserin</td>
<td>Double blind vs. placebo</td>
<td>30</td>
<td>15</td>
<td>BARS,SAS, BPRS, mLAS, HAM-D</td>
<td>14/15 on mianserin improved vs. 5/11 on placebo</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Retrospective chart review</td>
<td>8</td>
<td>15</td>
<td>BARS</td>
<td>5/8 patients experienced ≥ 2-point decrease on BARS global subscale. One patient had 1 point decrease, another did not respond</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Double blind vs. propranolol</td>
<td>90</td>
<td>15</td>
<td>BARS,SAS, BPRS, HAM-D</td>
<td>34% decrease in BARS global subscale with mirtazapine vs. 29% with propranolol and 11% with placebo</td>
</tr>
<tr>
<td>Ritanserin</td>
<td>Open trial</td>
<td>10</td>
<td>5-20</td>
<td>HAS, CGI</td>
<td>3/3 patients with resistant AIA improved</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Open trial</td>
<td>9</td>
<td>100</td>
<td>BARS,SAS, mLAS, PANSS, HAM-D, CGI</td>
<td>BARS global scores decreased to 0 in 5/9 patients. The other 4 patients had decreases ≥ 2 on the global subscale.</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Crossover trial vs. placebo</td>
<td>13</td>
<td>100</td>
<td>BARS,SAS, HAM-D, PANSS</td>
<td>Greater decreases in all BARS subscales with trazodone vs. placebo</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>Open trial</td>
<td>8</td>
<td>7.5</td>
<td>BARS, PANSS</td>
<td>BARS significantly improved in 6/8 patients</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>Double blind vs. propranolol</td>
<td>33</td>
<td>7.5</td>
<td>BARS,SAS, HAM-D, HAM-A, PANSS</td>
<td>26.1% decrease in mean BARS with zolmitriptan vs. 39.5% decrease with propranolol</td>
</tr>
</tbody>
</table>

*This table excludes case reports and may not be an all-inclusive list. ^Although positive results are reported, careful review of study methodologies is encouraged for adequate interpretation of results. BARS=Barnes Akathisia Rating Scale, SAS=Simpson Angus Scale, HAS=Hillside Akathisia Scale, BPRS=Brief Psychiatric Rating Scale, HAM-D=Hamilton Rating Scale for Depression, AIMS=Abnormal Involuntary Movement Scale, mLAS=modified Leeds Anxiety Scale, CGI=Clinical Global Impression, PANSS=Positive and Negative Syndrome Scale, HAM-A=Hamilton Rating Scale for Anxiety