Restrained use of antipsychotic medications: Rational management of irrationality

These drugs are commonly prescribed in conditions for which there is little evidence of benefit, but considerable risk of harm.
Antipsychotic medications (APMs) are a mainstay for managing major psychiatric illnesses such as schizophrenia and bipolar disorder, and can do enormous good for patients with these problems.

**FIGURE 1.** Annual US antipsychotic prescription trends, 1995 to 2008

However, in recent years newer agents, the atypical APMs, have been promoted widely for use in very different conditions, for which their efficacy is often not well established. These include the management of patients with Alzheimer’s disease, and as a core treatment for depression (Table 1). Besides their limited efficacy, these drugs can cause weight gain, raise blood sugar, prolong the Q-T interval, and increase cholesterol levels. They also significantly increase the risk of death in older patients.
Antipsychotic medications cause important adverse effects:

### TABLE 2. Adverse effects of APMs*

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Weight gain** &amp; metabolic effects</th>
<th>Extra pyramidal symptoms</th>
<th>QTc prolongation</th>
<th>Sedation</th>
<th>Orthostatic hypotension</th>
<th>Anticholinergic toxicity</th>
<th>Prolactin elevation</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>first generation APMs</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>haloperidol (Haldol)</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td></td>
<td></td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>perphenazine (Trilafon)</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>++</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>clozapine (Clozaril)</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td></td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>risperidone (Risperdal)</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
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<tr>
<td>second generation APMs</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>olanzapine (Zyprexa)</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>quetiapine (Seroquel)</td>
<td>+§</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td></td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>aripiprazole (Abilify)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>ziprasidone (Geodon)</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td></td>
<td></td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

* Authors’ consensus interpretation of pertinent evidence
** For weight gain, ++: 2-3 kg/month +: 1-2 kg/month
§ More triglyceride elevation than risperidone and aripiprazole
Antipsychotic medications and depression

Given their risks, these drugs should not be used for most patients to manage depression resistant to conventional antidepressant therapy.\(^2\)

First, make sure the patient actually has depression, based on DSM-IV criteria:\(^2\)

<table>
<thead>
<tr>
<th>Either 1 or 2 of the following must be present:</th>
<th>plus, these other symptoms to make a total of 5:</th>
</tr>
</thead>
</table>
| • depressed mood  
• markedly diminished interest or pleasure  | • change in sleep or appetite/weight  
• decreased energy  
• thoughts of worthlessness/guilt, or death/suicide  
• psychomotor retardation or agitation  
• poor concentration |

The patient must have these symptoms most of the day, nearly every day, for >2 weeks.

Then, treat with non-pharmacologic therapy (psychotherapy, or cognitive behavioral therapy), first line antidepressants, or both. ECT can be useful in some non-responsive patients, especially the elderly.

The algorithm below depicts several first, second, and third line treatments for depression, all of which are safer than use of an APM.\(^2-5\) SGAs are not recommended at any time because of tardive dyskinesia risk (see next page for explanation).

**FIGURE 2. Pharmacologic management of depression\(^2-5\)**

- Start with SSRI, bupropion, SNRI, or mirtazapine, 4-6 weeks. Choose agent based on anticipated side effects
- Remission?  
  - Y: Continue treatment  
  - N: Maximize dose of first agent
- Remission?  
  - Y: Continue treatment  
  - N: Combine SSRI + bupropion  
- Remission?  
  - Y: Continue treatment  
  - N: Augment with buspirone  
- Remission?  
  - Y: Continue treatment  
  - N: Switch to another first line agent
- Try another option above. If all fail to achieve remission, try 1 of 3 additional options, or refer to psychiatrist
- Augment with triiodothyronine  
- Try second line drug (TCA)  
- Combine venlafaxine + mirtazapine
• Aripiprazole, quetiapine, and olanzapine (in combination with fluoxetine) are FDA approved for depression therapy augmentation, but should be used when other augmentation strategies have failed.
  — There is robust evidence for mild efficacy for these SGAs (number needed to treat for improvement of 9) but the side effects, especially weight gain, are much more significant than with the other recommended augmentation strategies.7-8
• APMs are not FDA approved for monotherapy in depression.

In patients with **psychotic** depression (that is, with disruptive or dangerous delusions or hallucinations), an antipsychotic can be combined with an antidepressant.6

**FIGURE 3. Management of depression with psychotic features**

1. **Psychosis disruptive or dangerous**
   - SSRI + antipsychotic OR TCA + antipsychotic
   - Symptoms improved?
     - Y: Continue treatment
     - N: Switch to other combination
   - Symptoms improved?
     - Y: Continue treatment
     - N: Refer to psychiatrist

2. **Psychosis not disruptive or dangerous, or patient unwilling to take antipsychotic**
   - SSRI OR TCA
   - Symptoms improved?
     - N: Reconsider antipsychotic
     - Y: Continue treatment
In older patients with dementia, the use of antipsychotic medications increases the relative risk of death by 70%.\textsuperscript{9}

The risks of APMs often outweigh their benefits, especially when used for non-severe problems. In a randomized trial, only 20-30% of patients had improvement in symptoms when treated with an antipsychotic drug for dementia symptoms.\textsuperscript{10}

All APMs carry a black box warning about the risk of death:\textsuperscript{9}

\textbf{FIGURE 4.} Information from FDA Black Box Warning that appears on labeling for all antipsychotic medications\textsuperscript{9}

\begin{center}
\begin{tabular}{|l|}
\hline
\textbf{WARNING: Increased Mortality in Elderly Patients With Dementia-Related Psychosis} \\
\hspace{1cm} • Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. \\
\hspace{1cm} • The risk of death in drug-treated patients is 1.6–1.7 times that of placebo-treated patients. \\
\hspace{1cm} • Rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. \\
\hspace{1cm} • Most deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. \\
\hspace{1cm} • Treatment with conventional antipsychotic drugs also increases mortality. \\
\hline
\end{tabular}
\end{center}

It has been estimated that for every 100 patients with dementia treated with an antipsychotic medication, only 9 to 25 patients will benefit and 1 will die.\textsuperscript{10-11}

Despite their risks, antipsychotic medications are often used loosely in patients with dementia to manage a wide variety of behaviors, including wandering, socially inappropriate interactions, and difficulty sleeping. Many nursing home patients with dementia are prescribed APMs without a clear indication.
If these drugs must be used to manage agitation or aggressive behavior:

- identify the target behaviors being treated
- start at a low dose
- reassess regularly
  - to gauge the response of the targeted symptoms
  - to monitor for side effects
- use for the shortest time possible.

A systematic review found some APMs work better than others in patients with dementia with aggressive behavior requiring APM use.\(^\text{13}\)

**TABLE 3. Relative efficacy of APMs in treatment of dementia-related behaviors\(^\text{13}\)**

<table>
<thead>
<tr>
<th>Drug and starting dose</th>
<th>aripiprazole (5mg)</th>
<th>olanzapine (1.25mg)</th>
<th>quetiapine (12.5mg)</th>
<th>risperidone (0.25mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall symptoms*</td>
<td>Moderate-high evidence</td>
<td>Low or very low evidence</td>
<td>Moderate-high evidence</td>
<td>Low or very low evidence</td>
</tr>
<tr>
<td>Psychosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agitation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Measured by BEHAVE-AD, BPRS, or NPI: [www.assessmentpsychology.com/geriatricscales.htm](http://www.assessmentpsychology.com/geriatricscales.htm)

This review did not find any studies with ziprasidone for dementia-related symptoms.
Given the lack of benefit and substantial risks of APMs in older patients, whenever circumstances permit first try non-pharmacologic behavioral treatments. If these fail, medications can be added to manage severe persistent behavioral symptoms that present a real risk to the patient or others:

**FIGURE 6. Treatment algorithm for behavioral symptoms of dementia**

Attempt these non-drug approaches in all dementia patients with behavioral symptoms:
- **Reorient**: gently remind of person, place, time
- **Supervise**: provide companionship and observation
- **Calm**: offer exercise, music, massage, aromatherapy
- **Comfort**: address temperature, lighting, hunger, thirst
- **Reduce distress**: reduce noise, correct hearing/vision

<table>
<thead>
<tr>
<th>Dementia with no aggression</th>
<th>Dementia with mild aggression</th>
<th>Dementia with severe aggression</th>
</tr>
</thead>
<tbody>
<tr>
<td>No additional medications needed</td>
<td>Non-APM medications: SSRI, trazadone, memantine</td>
<td>APM medications: risperidone aripiprazole</td>
</tr>
</tbody>
</table>

**Restrained use of antipsychotic medications**: Rational management of irrationality
Antipsychotic drugs in other conditions

These drugs may be of use in some patients with post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD), but usually after other therapies (including psychotherapy) have been tried.

**Post-traumatic stress disorder:**
- For PTSD, first treat any sleep disturbance (algorithm below), then prescribe an SSRI.\(^{16}\)
- Sertraline and Paroxetine are the only FDA-approved medications for PTSD. Of the two, paroxetine has the better evidence-base, but also more side effects such as weight gain and sexual dysfunction.
- Resort to antipsychotic medications for PTSD patients with psychotic symptoms that persist on SSRIs, as depicted below:\(^{16}\)

**FIGURE 7. Management of post-traumatic stress disorder\(^{16}\)**

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**Obsessive-compulsive disorder:**
- First treat with an SSRI (most OCD patients will need maximum or higher doses); if poor response, try another SSRI.\(^{17}\)
- Continued symptoms may require an antipsychotic medication (risperidone is the most effective in OCD). Patients whose symptoms are severe enough to require consideration of an APM are likely to need the care of a psychiatrist.
Screening and monitoring are necessary

Whatever the indication, all patients prescribed an APM will require a number of screening tests both at baseline and at regular intervals, to monitor adverse effects.¹⁸

**TABLE 4. Monitoring adverse effects in patients taking APMs**

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>What to assess</th>
<th>Screening: at baseline, and then:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolic effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall weight gain</td>
<td>weight and BMI</td>
<td>monthly x 3, then quarterly</td>
</tr>
<tr>
<td>central weight gain</td>
<td>waist circumference</td>
<td>annually</td>
</tr>
<tr>
<td>diabetes</td>
<td>fasting glucose, or HgbA1c</td>
<td>3 months, then annually</td>
</tr>
<tr>
<td>hyperlipidemia</td>
<td>fasting lipid profile</td>
<td>3 months, then every 5 years or less</td>
</tr>
<tr>
<td><strong>Neurologic effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>extrapyramidal symptoms</td>
<td>involuntary movements</td>
<td>every visit</td>
</tr>
<tr>
<td>sedation</td>
<td>daytime somnolence</td>
<td>every visit</td>
</tr>
<tr>
<td><strong>Cardiovascular effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QT prolongation</td>
<td>QT interval on EKG</td>
<td>with addition of other QT prolonging drugs*</td>
</tr>
<tr>
<td>orthostatic hypotension</td>
<td>dizziness or BP drop with standing</td>
<td>every visit</td>
</tr>
<tr>
<td><strong>Other effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prolactin elevation</td>
<td>galactorrhea, amenorrhea, sexual dysfunction, gynecomastia</td>
<td>every visit</td>
</tr>
<tr>
<td>anticholinergic toxicity</td>
<td>blurry vision, dry mouth, sedation, urinary retention, constipation</td>
<td>every visit</td>
</tr>
</tbody>
</table>

* A list of QT prolonging drugs can be found at: [www.qtdrugs.org](http://www.qtdrugs.org)
Cost

All second generation antipsychotics are expensive.

Antipsychotics are the 5th most costly medication class in the U.S., with annual spending of >$16 billion.\(^\text{19}\) Even with low doses or generics, the monthly cost of all these agents may be unaffordable for many patients.

**FIGURE 8.** Monthly cost of antipsychotic medications based on defined daily dose from the World Health Organization

![Cost Analysis Chart](image)

Listed doses reflect dosing equivalents, and are not recommended starting doses in the elderly.

Drug prices obtained from drugstore.com

References:


Additional references documenting these recommendations are provided in the evidence document accompanying this material, also available at www.RxFacts.org.
About this publication

These are general recommendations only; specific clinical decisions should be made by the treating physician based on an individual patient's clinical condition.

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