Appropriate Use of Antipsychotics

Prescriber and Pharmacist Frequently Asked Questions

As part of the Appropriate Use of Antipsychotic project, this FAQ was developed for health professionals by a team of experienced clinicians, with the intention of provoking discussion and thought, rather than providing simplified answers to complex problems.

You may find the answers to these questions are all various forms of "It depends." This is intentional. To simplify the answers to these questions (or to ask simpler questions) defeats the purpose of having a discussion at all. The reader is encouraged to read these comments (and the linked evidence), and compare these scenarios with their own clinical practice. Patients, families, caregivers and health professionals will each have their own tolerance to risk, tolerance for "acceptable" behaviors, and varying degrees of expertise and experience in dealing with responsive behaviors of dementia.

1. What evidence is there that antipsychotics are harmful?

Antipsychotics have been associated with increased risk of stroke, mortality, falls and community acquired pneumonia when used in patients with dementia. A 2011 Systematic Review[i] described these risks and prompted FDA warnings. The most comprehensive evidence for antipsychotic usage and associated harms was provided by the CATIE-AD trial.[ii] In addition, we know from DART-AD follow-up[iii] that *stopping* long term antipsychotics can reduce mortality.

FDA blackbox warnings for risperidone include the following information:

> **Serious Warnings and Precautions**
> Increased Mortality in Elderly Patients with Dementia. Elderly patients with dementia treated with typical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of thirteen placebo-controlled trials with various atypical antipsychotics

(modal duration of 10 weeks) in these patients showed a mean 1.6-fold increase in the death rate in the drug-treated patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious in nature (e.g., pneumonia). See WARNINGS AND PRECAUTIONS — Special Populations, Use in Geriatric Patients with Dementia of the Alzheimer Type.

Overall Mortality
Elderly patients with dementia treated with atypical antipsychotic drugs have an increased mortality compared to placebo in a meta-analysis of 13 controlled trials of various atypical antipsychotic drugs. In six placebo-controlled trials with RISPERDAL® in this population, the incidence of mortality was 4.0% for RISPERDAL®-treated patients compared to 3.1% for placebo-treated patients.

Antipsychotic Side Effects
Antipsychotic side effects are numerous and frequent in the elderly, and include anticholinergic reactions, parkinsonian events, tardive dyskinesia, orthostatic hypotension, cardiac conduction disturbances, reduced bone mineral density, sedation and cognitive slowing.[iv] There is a 2-3 times higher rate of adverse drug effects in older adults than in adult patients younger than 30 years.[v] Other side effects include over-sedation, insomnia, weight gain, dizziness, confusion, increased risk of falls, illogical thinking, blurred vision, delirium, constipation, urinary tract infections, rash, nausea and GI upset.[vi]

In addition, atypical antipsychotics worsen cognitive function at a magnitude consistent with one year's deterioration compared to placebo.[vii] Worsening cognitive function produces anxiety, increases responsive behaviours and interferes with social engagement and the ability to communicate.

Alberta long term care (LTC) centres find that residents usually improve over the weeks to months that follow antipsychotic discontinuation. Many regain abilities such as speech, the ability to feed themselves and assist with their own care. Some begin walking again, others are simply more alert – or may recognize family members again. The unnecessary acceleration of cognitive decline – along with minimal benefit– is perhaps the most harmful effect of inappropriate antipsychotic use.

2. Which antipsychotics are indicated for treatment of BPSD/Responsive Behaviours?

Several antipsychotics have been studied with various degrees of efficacy including risperidone, olanzapine, quetiapine, and haloperidol. Results were mixed for all of these agents, with some trials showing no benefit. More recently, aripiprazole[viii] was found to be *ineffective* for psychotic symptoms associated with Alzheimers Dementia. A useful summary of antipsychotics for BPSD from 2012 (does not include aripiprazole) can be found here:
http://www.rxfiles.ca/rxfiles/uploads/documents/Psych-BPSD-Newsletter.pdf

Interestingly, only one antipsychotic has an official indication for management of responsive behaviors in dementia – risperidone. As we will discuss further, this is interesting, as risperidone is thought to be the most "typical" of the atypical antipsychotics, and thus may have more adverse effects in elderly patients. As per product monograph: RISPERDAL® is indicated for the short-term symptomatic management of aggression or psychotic symptoms in patients with severe dementia of the Alzheimer type unresponsive to non-pharmacological approaches and

when there is a risk of harm to self or others. Other behavioral disturbances seen in this patient population as well as disease stages remained unaffected by RISPERDAL® treatment.

3. Are there "preferred" antipsychotics for treatment of Responsive Behaviours?

Selection of agents should consider efficacy, safety profile and patient specific factors. Side effect profiles for particular agents can be generally compared to weigh risks of common adverse effects:

Side Effect	Likelihood
Weight Gain/ Metabolic Effects	OLZ > QUE > RISP
Extra-Pyramidal Symptoms (EPS)	RISP* > OLZ > QUE
Anticholinergic /Cognitive Effects	QUE = OLZ > RISP
Tardive Dyskinesia	RISP > OLZ > QUE
Sedation	QUE** = OLZ > RISP

**Increased EPS at high doses of risperidone (2-4mg/day)*
***Low doses of quetiapine are more sedating*
from RxFIles, 2014 (Dementia in the Elderly)[ix]

Consider what agents have been trialed before, and if the previous trial was of adequate dose and duration. Try to find out why the previous agent was stopped – lack of efficacy or adverse reaction or other reason (cost to patient, noncompliance etc.). Assess if a re-trial would be appropriate (i.e. symptoms initially responded but were manageable without treatment before, symptoms are now *more* severe requiring treatment). If we can assume that the primary desired effect of an antipsychotic is to be used as a chemical restraint, then it is a matter of achieving the desired "restraint" effect while minimizing the adverse reactions.

Patient-specific factors should be considered, including risk or history of movement disorders (i.e. Parkinson's disease) and stroke or TIA, as well as co-morbidities and other medications that may place the patient at a higher risk of experiencing adverse effects such as cardiac disease, Lewy Body dementia, renal disease, other antidepressants or CNS-active drugs. In all cases, risk vs. benefit must be weighed individually.

4. How would you define an "appropriately" used antipsychotic?

There are many valid indications for antipsychotics, primarily primary mental health disorders, even if the patient also has dementia. Several common disorders are described below, and further information on appropriate indications can be found in the clinical indications document in the AUA Toolkit and in the Alberta AUA Guideline.

Specific practice points from a practicing geriatric psychiatrist:

- Schizophrenia and other Primary Psychotic Disorders
  - Reduction in positive symptoms with aging
  - There may be 'intra-psychic benefits' to development of delusions in some individuals
  - Antipsychotics are the most effective (first line) mainstay treatment for geriatric patients with both late onset and early onset psychosis
  - Maintenance treatment is required for older patients with schizophrenia, though dose reduction may occur with age
  - In patients refractory to other first line treatments, antipsychotics may be necessary to manage sleep disturbance (which is a risk factor relapse) and co-morbid anxiety or mood disturbance
- Bipolar Disorder
  - Antipsychotics are used as primary or adjunctive treatments for bipolar disorder
  - It is a MYTH that bipolar disorder burns out with age (it may actually escalate in terms of frequency and severity of episodes); evidence exists for maintenance treatment to avoid future relapses
- Personality Disorders
  - Antipsychotics are used to augment behavioral and other pharmacological management strategies in various personality disorders
  - Discontinuation of antipsychotics may lead to emergence of impulsivity, mood lability, disorganized or psychotic behavior

In the context of the AUA project, the target population is those residents with severe dementia with responsive behaviors that place themselves or others at risk; or for those patients with positive symptoms such as psychoses, delusions or hallucinations that are deemed to be severe based on the degree of danger, suffering, or excess disability to the resident.

Regardless of indication, it is most appropriate to ensure that all antipsychotics are reviewed regularly to assess their efficacy and risks. The frequency of reassessment required may vary based on clinical need, but at a minimum, monthly assessment of antipsychotics is mandated by the 2008 Alberta Continuing Care Health Service (CCHS) Standards chemical restraint policy. For specific residents, it may be appropriate to reassess treatment on a weekly or biweekly basis, particularly during dose changes. The use of a behavior and mapping tool is recommended in order to compare behavior changes as objectively as possible. A variety of behaviour mapping tools are included in the responsive behaviours section of the AUA Toolkit.

5. How do you determine a "safe" dose of antipsychotic to use?

Rxfiles and the Clinical Handbook of Psychotropic Drugs have some excellent guidelines for dosing antipsychotics in the elderly – see summary chart below. As there is not a defined target dose to achieve a desired effect, the answer is to use as small a dose as is reasonable. Clinical trials that determined effective doses of medications were balanced by increased harms; thus there are no well-defined, accepted, "safe" doses.

The old adage rings true: Start low, go slow. Remember that elderly residents will be more sensitive to the effects of medications, and will have a higher variability in clinical response due to pharmacodynamics changes in CNS receptors. As well, pharmacokinetic factors specific to the elderly can include reduced absorption, greater volume of distribution, and decreased clearance through CYP enzymes and renal elimination. Dose adjustments often are needed throughout the course of therapy in order to find the most effective dose with manageable adverse effects. **The lowest effective dose is always the goal.**

Medication	Dose Range	Initial Dose Usual Maintenance Dose
Risperidone	0.25-2.0mg/day*	Initial: 0.125mg – 0.25mg daily Usual: 0.5mg – 2.0mg daily
Quetiapine	12.5-200mg/day*	Initial: 12.5mg daily Usual: 25-100mg daily
Olanzapine	1.25-10mg/day*	Initial: 1.25mg daily Usual 2.5-7.5mg daily
Haloperidol	0.25-2.0mg/day	Initial 0.25mg BID-TID Usual: 0.25mg-1.0mg BID

**may divide doses BID*

Dosing information from RxFIles, 2014 (Dementia in the Elderly)[x]

6. What alternative pharmacological treatments are recommended for responsive behaviours?

The term "Responsive Behaviors" speaks to the movement in the nomenclature away from the more traditional "Behavior and Psychological Symptoms of Dementia (BPSD)" terminology and approach. The idea is that if you can identify and manage the stimuli (real or perceived) that the behaviors are in response to, the resident's behaviors will decrease or stop. There are many person-centered and non-pharmacological strategies for this listed in the AUA Toolkit[xi].

Pharmacological treatment may be needed for underlying medical causes of responsive behaviors, including pain, depression, anxiety, delirium, infection, or constipation. Depending on comorbidities or contributing factors to behaviors, it may be appropriate to consider treatment with other CNS medications such as analgesics, antidepressants, anxiolytics, or sedatives – with the caution that all of these medications can also be associated with increased risk and harm to patients. Rxfiles[xii] provides a good summary of the risks and benefits for these medications in patients with dementia. As well, the Alberta College of Family Physicians reviewed the evidence for the use of benzodiazepines in the management of agitation in dementia[xiii].

Medication side-effects may trigger behaviours, requiring medication discontinuation or adjustment.

Another important consideration is the ***prescribing cascade***. Prescribing cascades are defined as the prescribing of a new medication to treat symptoms that have arisen from an unrecognized

adverse effect of an existing medication. A common, simple example might be verapamil started for atrial fibrillation which causes constipation, which results in a laxative being required. In this case, the benefit of verapamil for management of the heart rate may outweigh the risk / inconvenience of laxatives. However, prescribing cascades may also be more complex, as illustrated by the following example:

Amitriptyline prescribed for headaches ➡ urinary retention & incontinence ➡ oxybutynin prescribed for incontinence ➡ worsened cognitive function, increased behaviors +/ - delirium ➡ antipsychotic prescribed.

In this example, does the benefit of amitriptyline for headaches outweigh the risks of additional anticholinergic medications and antipsychotic medications? In most individuals, probably not - alternatives for managing headaches should be investigated.

7. How long should treatment with an antipsychotic be continued?

The answer should be *only as long as behaviors persist*. In reality, we know it is never that easy - the key to this question is ongoing frequent reassessment. As per Alberta Continuing Care Health Standards, every resident on an antipsychotic should be re-evaluated at least q30 days. Realistically, we would advocate for a more frequent reassessment based on individual needs – for example, it is appropriate to reassess within 1-2 weeks following starts, stops or dose changes. Consider a structured approach to your reassessment to include, in this order:

a. **Indication** – is the antipsychotic still needed?
b. **Efficacy** - Have the behaviors resolved? Improved? How do I know?
c. **Safety** – Have there been any adverse effects? Has anything changed with the resident that would increase their risk for adverse effects? Determine if safety concerns require medication change or continued monitoring.
d. **Compliance** – Are there any issues with administration (ie. crushing or medication refusal) or accessibility (medication financial concerns)?

If there is no clear ongoing indication, there is no need to assess any further – consider tapering off medication. If there is an indication, then assess efficacy. If there has been no improvement, consider tapering off medication. If there is both indication & efficacy, consider safety & compliance concerns, which may be addressed in a variety of ways (i.e. drug discontinuation, dose decrease, rotation to another agent or class of medication).

It's crucial to assess susceptibility of the client to harm posed by adverse effects of antipsychotics. If, for example, a client has a history of falls, their risk on antipsychotics for any reason will be increased. Or if another sedating drug has been added for another valid indication, perhaps the antipsychotic dose now needs to be lowered to prevent over sedation. In order to balance the harm of these agents, we need to be sure there is ongoing benefit to the resident. Some behaviors will decrease in severity & may resolve as dementia progresses.

8. Is it effective to use antipsychotics on a PRN basis?

"Effective" is a relative term. Antipsychotics used to inhibit a particular behavior or restrict movement and that are not the standard treatment for a resident's medical or psychiatric condition are defined as chemical restraints. A PRN dose of a medication may be effective as a restraint for a particular instance, but ineffective if the goal is to prevent severe and ongoing

behaviors. Once appropriate non-pharmacological options to prevent responsive behaviors have been implemented, the need for PRN chemical restraints is dramatically decreased. Remember that the strongest clinical evidence is for regularly scheduled dosing of antipsychotics in the management of psychotic symptoms of dementia. Thus, this is generally preferred over PRN dosing of antipsychotics.

On the other hand, PRN use may be an appropriate option for the short term management of psychosis, delusions and hallucinations associated with delirium. Management of delirium[xiv] is not within the scope of this discussion, but a wide variety of resources are available within the AUA Toolkit. Be cautious of the risk of overuse with combined PRN and scheduled doses, as well as with combination therapy. There is no evidence for using a combination of two different antipsychotics, and an exponentially increased risk of adverse effects. **All PRN orders should be regularly reassessed for appropriateness, and discontinued if they have not been used within the previous 30 days, as per CCHS standards.**

9. How do you treat Extra-Pyramidal Symptoms (EPS) caused by antipsychotics?

Generally, using the lowest possible dose for the shortest possible timeframe is the best way to prevent EPS in residents on antipsychotics for responsive behaviors of dementia. However, for residents requiring long term or high dose antipsychotics, management of these adverse effects may be required. Whenever possible, attempt to lower the dose, switch agents, or discontinue the antipsychotic. If there is a need to stop therapy due to adverse effects, taper the dose slowly in order to avoid withdrawal symptoms (dizziness, nausea, vomiting, headache, tremors, insomnia & anxiety). Monitor for recurrence of target symptoms or behaviours or the emergence of new ones. In rare cases, tardive dyskinesia symptoms may develop upon discontinuation. These symptoms may resolve over a period of weeks to months, or may be permanent.

Consideration should be given to involving experts in geriatric mental health or psychiatry to assist with management of EPS in patients with known underlying mental health indications for antipsychotics. In some severe versions of tardive dyskinesia and dystonias, a dose *increase* or addition of another agent (ie. benztropine or a benzodiazepine) may actually cause suppression of these movements and be a safer option to alternatives like dose reduction or discontinuation. Be cautious when discontinuing long term antipsychotics in residents with unclear indications or unknown psychiatric histories. Make all attempts possible to understand what underlying conditions and behaviors may be untreated as a result of stopping therapy.

10. How does limited life expectancy and goals of care (GOC) affect decision making with respect to using antipsychotics?

It is useful to consider the life expectancy and goals of care of an individual when assessing the potential benefits and risks of any drug therapy. Overall frailty, comorbidities, polypharmacy and physiological age are important considerations. Consider the overarching purpose of medical therapy: **"To cure sometimes, to relieve often, to comfort always."**

Antipsychotics are not intended to cure; they are to relieve symptoms. A more conservative approach may be appropriate if patients are not distressed by the responsive symptoms. When the focus of care shifts to comfort only, medications should be reassessed when no longer useful

or more harmful than beneficial. A process of routine structured medication reviews is essential to identifying these opportunities.

Similarly, when assessing the risk of long term adverse effects of antipsychotics, it can be useful to consider life expectancy and goals of care. Consider the following examples:

Are metabolic side effects of antipsychotics a relevant consideration in the elderly? Metabolic side effects (weight gain, hyperlipidemia, diabetes) of antipsychotics are more common with the higher doses and long term (years) of therapy required in patients using these agents for schizophrenia or other chronic mental health conditions. For many patients taking "appropriate" (low dose, short term) antipsychotics for responsive behaviors of dementia, these effects are not likely to be a concern. Monitoring plans for these residents should be reasonably non-invasive. For example, appropriate laboratory monitoring (CBC, creatinine, electrolytes) can be timed with other required bloodwork. Glucose monitoring may be done more frequently if the resident has poorly controlled diabetes, and glycemic targets may be individualized.

Is QT prolongation of concern with antipsychotic use in the elderly? Again, this is more likely with higher dose and longer term therapy, or if used in conjunction with other QT prolonging medications.[xv] Consider individual history of arrhythmias or heart disease. ECG monitoring may be appropriate in some patients at higher risk, but may not be a high priority or reasonable for patients with severe dementia. The care team should discuss appropriate and reasonable monitoring plans for individual patients.

11. What strategies would you recommend to address a care team member or family member "requesting" an antipsychotic for a resident?

- Ask for more information: What is the resident doing? When does this occur? What else could be going on physically, medically, socially or in the environment? What non-pharmacologic strategies have you tried?
- Review specific behaviors of concern. Assess if antipsychotics may help. Assess if non-pharmacological strategies can be used. Educate, provide appropriate information if needed.
- If the requests are perceived as a matter of routine (e.g. "that's what we usually use for aggression"), change management strategies may be useful. Seek out help amongst the facility's management or education teams, and refer to resources in the AUA Toolkit.
- In practice, when dealing with family members who may be distraught or embarrassed over the behaviors of their loved ones, it may be helpful to provide education on the dementia disease process. A supportive, considerate approach will help to alleviate caregiver anxiety; written materials may be helpful when antipsychotic use places client safety and comfort at risk. (See AUA Toolkit for resources)

12. How do you weigh the safety needs of staff and residents vs. the risk of antipsychotic use in the care of an aggressive resident?

While we advocate for the most appropriate use possible of antipsychotics in geriatric patients, there are always exceptions to every rule or guideline. When antipsychotics are *effective* to treat agitation, psychosis or aggression of severe intensity, preliminary studies suggest the potential for relapse of behaviors with antipsychotic discontinuation is high. Therefore, the risk of relapse

in this subset of patients with dementia needs to be weighed against the risk of metabolic, neurological, mortality and other adverse consequences of medication continuation, as well as the risk for injury to caregivers and other residents with medication discontinuation.

Inappropriate reduction of medications may lead to psychiatric symptoms that are distressing for residents and caregivers and may also pose a safety risk to the resident, co-residents and caregivers (creating medico-legal consequences for the facility and staff). De-stabilization of psychiatric illnesses may also necessitate admission to hospital for further management.

When safety is potentially at issue, reduce antipsychotic medications slowly, by ¼ to ½ the dose per month until optimal balance is achieved between side-effect reduction and symptom control. Continue to monitor for an increase in agitation, psychosis or aggression over the following months as levels of antipsychotics in the brain may take months to stabilize or clear.

Other valuable references

RxFiles Dementia Overview October 2014: http://www.rxfiles.ca/rxfiles/uploads/documents/Dementia-Newsletter-Overview-Booklet-WEB.pdf

Alberta College of Family Physicians Tools for Practice BZD use in behavioral symptoms of dementia: https://www.acfp.ca/wp-content/uploads/tools-for-practice/1425325257_tfp133benzosagitationdementiafv.pdf

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J. Liu B.Sc. (Pharm), CGP, APA

G.Cummings B.Sc/ (Pharm), ACPR

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[xv] http://www.rxfiles.ca/rxfiles/uploads/documents/Dementia-Newsletter-Overview-Booklet-WEB.pdf