



Antipsychotics in Dementia

What's all the fuss?

Judy MacDonald RPh BSc Pharm

Dr. Ashok Krishnamoorthy MD MRCPsych FRCPC ABAM MS (Neuro Psych)



Learning Objectives

- Recognize common behavioural & psychological symptoms of dementia
- Describe appropriate use of antipsychotic medication
- Identify some considerations for selecting antipsychotic medication
- Identify potential side effects of antipsychotic medication
- Describe how to initiate, taper and discontinue antipsychotic medication

Expected Progression of Dementia

Early Stages

Memory loss
Language difficulties
Irritable
Withdrawn
Abusive language
Mood swings

Middle Stage

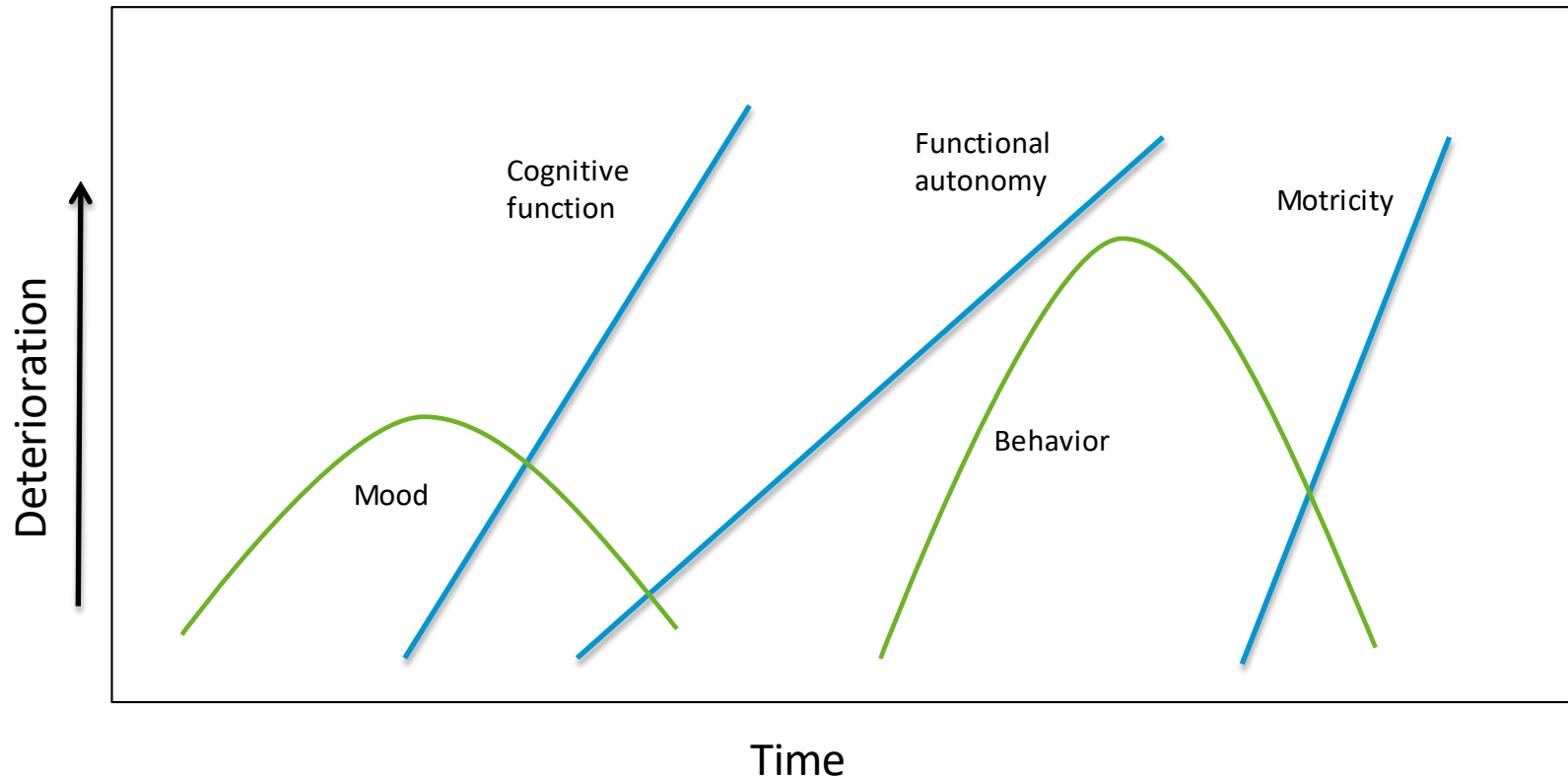
Delusions
Hallucinations
Agitation/Anxiety
Aggression
Depression
Harm to self or others

Late Stage

Loss of Speech
Moving difficulty
Incontinent
Swallowing difficulty
Total Care



Symptomatic domains over time



Ref: Gautier, et al. 1996, Gelinas and Auer. 1996; Eastwood and Reisberg. 1996; Barclay, et al.. 1985

Appropriate Use of Antipsychotics

Confirmed Mental Health diagnosis

- Schizophrenia or Huntington's Chorea
- Bi Polar disorder
- Major depressive disorder

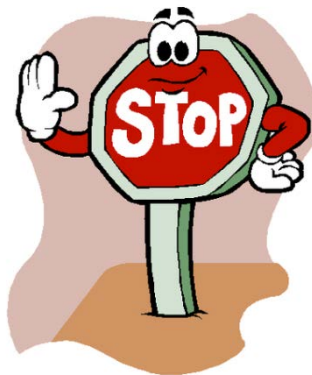
Severe Psychotic Symptoms

- Delirium
- Physical aggression with risk of injury to self or others

- Short term management means months not years
- Considered a chemical restraint with the goal to address the underlying reasons for the agitation or aggression
- Do not work every time

Behaviors with limited benefit to Antipsychotics

- Wandering/exit seeking
- Restlessness/pacing
- Insomnia
- Irritable mood
- Poor self-care
- Impaired memory
- Eating inedible objects
- Hoarding/hiding items
- Calling out/ screaming
- Repetitive actions (clapping)
- Fidgeting
- Inappropriate elimination
- Inappropriate dressing/undressing
- Rummaging
- Interfering with other residents
- Insomnia



Meds that may cause altered mental symptoms in the elderly

- Anticholinergics (confusion)
- Antiparkinsonian agents (psychosis)
- Benzodiazepines (cognitive impairment, delirium)
- Cardiac medications (confusion)
- Corticosteroids (delirium)
- Opioid narcotics (confusion, delirium)
- Stimulants (confusion, paranoia, anxiety)

Medications with anticholinergic Properties

- Antipsychotics
- Antidepressants
- Antihistamines
- Gout Medication
- Benzodiazepines
- Opioids
- Muscle Relaxants

Physical Disorders that may cause altered mental symptoms

- Hyper or hypoglycemia
- Hyper or hypothyroidism
- Electrolyte imbalances
- Parkinson's disease
- Vitamin B12 deficiency
- Untreated pain
- AIDS
- Brain tumour
- Stroke
- Seizure disorder
- Sleep deprivation

What to consider before Medication

Responsive Behaviors:

- Consistent care providers
- Flexible breakfast times to allow residents to wake up and eat when ready
- Reduce overstimulation

Sleep Disturbance

- During the day increase light and activity
- In the evening engage residents in quiet activities and provide a warm non-caffeinated beverage. Reduce light levels
- At night reduce noise and avoid waking residents for scheduled care unless necessary

What to consider before Medications

Delirium Prevention:

- Reduce Anticholinergic pill burden
- Hydration and nutrition
- Pain management
- Reduce overstimulation
- Vision and hearing aids
- Maintain mobility
- Reduce use of restraints

Antipsychotics (P.I.E.C.E.S. 6th Ed)

Detect

Select

Effect

DETECT

P.I.E.C.E.S. Psychotropic Framework

When should antipsychotics be considered?

DETECT: When should antipsychotics be considered?

Clinical purpose:

- Psychotic disorders
- Dementia with specific BPSD target symptoms (aggression, psychosis)
- Mood Disorders
- Delirium

DETECT: When should antipsychotics be considered?

Chemical Restraint

- Are medications used with the specific intent to sleep cycle. beyond that required to establish a normal reduce a patient's mobility or promote sedation
- This should not be confused with medications used to treat drug responsive behavioral / specific medical and psychiatric diagnosis. neuropsychiatric symptoms associated with (www.bcbpsd.ca)

Choosing Wisely Canada

Do not use antipsychotics as first choice to treat behavioural and psychological symptoms of dementia.

People with dementia often exhibit challenging behavioural symptoms such as aggression and psychosis. In such instances, antipsychotic medicines may be necessary, but should be prescribed cautiously as they provide limited benefit and can cause serious harm, including premature death. Use of these drugs should be limited in dementia to cases where nonpharmacologic measures have failed, and where the symptoms either cause significant suffering, distress, and/or pose an imminent threat to the patient or others. A thorough assessment that includes identifying and addressing causes of behaviour change can make use of these medications unnecessary. Epidemiological studies suggest that typical (i.e., first generation) antipsychotics (i.e., haloperidol) are associated with at least the same risk of adverse events. This recommendation does not apply to the treatment of delirium or major mental illnesses such as mood disorders or schizophrenia.

Select

P.I.E.C.E.S. Psychotropic Framework

How do I contribute to the selection of the right medication?

SELECT: Selecting the right medication

Drug interactions

- Pharmacokinetic- a drug effects the absorption, distribution or metabolism/excretion of another to alter the quantity of medication at the active site
- Pharmacodynamic- two or more drugs have additive or opposite beneficial or adverse effects at their receptors

SELECT: Selecting the right medication

Examples (Pharmacokinetic interactions with antipsychotics)

- Quetiapine is primarily metabolised by an enzyme CYP3A4
- Inducers (e.g. phenytoin and carbamazepine) will cause faster metabolism and less effect of quetiapine and higher doses may be required
- Inhibitors (e.g. erythromycin, grapefruit juice) can slow down the metabolism of quetiapine and lead to enhanced effects both beneficial and adverse

SELECT: Selecting the right medication

Examples (Pharmacodynamic drug interactions)

- Additive sedation: opioids, benzodiazepines, zopiclone, anti-depressants, sedating anti-histamines
- Additive hypotension and dizziness: diuretics, ACE inhibitors, - beta blockers, calcium channel blockers, tamsulosin, terazosin
- Additive anti-terazosin -cholinergic effects: oxybutynin, opioids, inhaled tiotropium /ipratropium
- Additive parkinsonian effects: SSRIs, metoclopramide, prochlorperazine

SELECT: Selecting the right medication

QTc Prolongation (detected by ECG)

- Anti-psychotics have potential to prolong QTc, can lead to Torsade de Points, syncope and sudden death
- Risk factors: female, older age, bradycardia, low potassium and magnesium levels, liver or cardiac disease
- Effects of drugs may be additive extensive list includes: domperidone, SSRI e.g. citalopram, antibiotics e.g. clarithromycin, moxifloxacin, cardiac medications e.g. amiodarone, sotalol

SELECT: Selecting the right medication

Determining the right medication for each person

- Diagnosis
- Response to previous medication trials
- Allergy status
- Medical history and current problems
- Renal and liver function
- Complete medication list
- Vitals (postural hypotension?)
- Dosing frequency

SELECT: Selecting the right medication

Typical Antipsychotics	Atypical Antipsychotics	Antipsychotic Depots
chlorpromazine (Largactil)	aripiprazole (Abilify)	fluphenazine LA (Modecate)
fluphenazine (Moditen)	asenapine (Saphris)	flupenthixol LA (Fluanxol Depot)
flupenthixol (Fluanxol)	clozapine (Clozaril)	haloperidol LA (Haldol LA)
haloperidol (Haldol)	lurasidone (Latuda)	paliperidone palmitate (Invega Sustena)
loxapine (Loxapac)	olanzapine (Zyprexa/Zydis)	risperidone (Risperdal Consta)
methotrimeprazine (Nozinan)	paliperidone (Invega)	zuclopenthixol LA (Clopixol Depot)
perphenazine (Trilafon)	quetiapine (Seroquel)	
pimozide (Orap)	risperidone (Risperdal)	
thiothixene (Navane)	ziprasidone (Geodon)	
zuclopenthixol (Clopixol)		
zuclopenthixol acuphase (Clopixol Acuphase)		
other – ie. sulpride (Dogmatil)		

SELECT: Selecting the right medication

Atypical Antipsychotics

- Risperidone, aripiprazole, and olanzapine have the strongest evidence to treat psychosis and agitation/aggression in dementia^{1,2}
- Number needed to treat for significant improvement 5-14
- Odds ratio for significant improvement compared to placebo: 1.5-2.5

1. Schneider, Am J Geriatr Psychiatry, 2006

2. Ballard, Coch Database Syst Rev, 2008

3. Fontaine, J Clin Psych, 2003

4. Tariot, Am J Geriatr Psychiatry, 2006

5. Verhey, Dementia Geriatr Cogn Disord, 2006

SELECT: Selecting the right medication

Antipsychotics:

- classified based on chemical class and neuroreceptor affinity profiles
- antipsychotic activity
- absence of deep coma or anesthesia in large doses
- absence of physical or psychic dependence
- term 'tranquilizer and neuroleptic' are outmoded

SELECT: Selecting the right medication

Atypical Antipsychotics (AA)

Medication*	Initial Oral Dose (mg)	Dosing Frequency	Formulation	Titration Dose (mg) and Schedule	Average total per day (mg)	Common Side Effects	Medication Administration
risperidone (Risperdal)	0.25	daily to bid	<ul style="list-style-type: none"> • tablet • "M" Tablet • oral liquid 	0.25 q3 to 7 days	1	<ul style="list-style-type: none"> • sedation • confusion • postural hypotension • parkinsonian symptoms** • falls 	<ul style="list-style-type: none"> • Measure liquid doses carefully • M tablets – remove from package just prior to administration to avoid dissolving prematurely
olanzapine (Zyprexa)	1.25-2.5	daily at hs to bid	<ul style="list-style-type: none"> • tablet • oral dissolving tablet (Zydis) 	1.25-2.5 q3 to 7 days	5	<ul style="list-style-type: none"> • as above 	<ul style="list-style-type: none"> • Oral dissolving tablets – remove from package just prior to administration to avoid dissolving prematurely
quetiapine (Seroquel)	12.5-25	bid to tid hs if XR	<ul style="list-style-type: none"> • tablet • slow release (XR) 	12.5-25 q3 to 7 days	150	<ul style="list-style-type: none"> • as above 	<ul style="list-style-type: none"> • Do not crush XR tablets
aripiprazole (Abilify)	2	daily	<ul style="list-style-type: none"> • tablet 	2-5 qweekly	10	<ul style="list-style-type: none"> • as above with exception of sedation; • may cause restlessness early in treatment 	<ul style="list-style-type: none"> • Nil
Other							

*Please consult with the product monograph for more detailed information.

** Parkinsonian symptoms include rigidity, slow movements, shuffling gait, flat affect, and tremor.

SELECT: Selecting the right medication

Typical Antipsychotics

Medication*	Initial oral dose (mg)	Dosing Frequency	Formulation	Titration Dose (mg) and Schedule	Average Total per day (mg)	Common Side Effects	Medication Administration
haloperidol (Haldol)	0.25-0.5	daily to bid	<input checked="" type="checkbox"/> oral <input checked="" type="checkbox"/> liquid (if available) <input checked="" type="checkbox"/> short-acting IM	0.25-0.5 q3 to 7 days	3	<input checked="" type="checkbox"/> sedation <input checked="" type="checkbox"/> anticholinergic side effects <input checked="" type="checkbox"/> tardive dyskinesia <input checked="" type="checkbox"/> dystonia (leaning) <input checked="" type="checkbox"/> drooling <input checked="" type="checkbox"/> akathisia (restlessness) <input checked="" type="checkbox"/> Parkinsonian symptoms** <input checked="" type="checkbox"/> falls	***caution do not confuse short acting IM with depot formulations***
loxapine (Loxapac)	2.5	bid	oral and intramuscular formulation	2.5-5	20	<input checked="" type="checkbox"/> as above	<input checked="" type="checkbox"/> nil

*Please consult with the product monograph for more detailed information.

** Parkinsonian symptoms include rigidity, slow movements, shuffling gait, flat affect, and tremor.

1. Key Messages/Considerations :

- ☒ Start low and go slow;
- ☒ Strive for a good clinical trial - increase dose only until clinical effectiveness is achieved;
- ☒ For acute use, see following link in the algorithm:
http://bcbpsd.ca/docs/Pharmacological_Treatment_of_Responsive_Behaviours.pdf
- ☒ Avoid in Lewy Body Dementia or Parkinson's Disease if possible;
- ☒ The risk of adverse events including death and stroke associated with typical antipsychotics are equal or greater than the risks of atypical antipsychotics;

Effect

P.I.E.C.E.S. Psychotropic Framework

How do I monitor the response and side effects?

EFFECT: Monitoring the response

Safety and Antipsychotics

- Over-sedation
- Postural Hypotension
- Impaired cognition
- Falls
- Weight gain
- Hyperglycaemia
- QTc prolongation
- Extra-pyramidal symptoms (EPS)
 - Tardive Dyskinesia
 - Cerebrovascular events
 - Mortality

(VCHA, Antipsychotic Guidelines BPSD, 2011)

EFFECT: Monitoring the response

Side Effect Profiles

	EPS	Hyperlipidemia	Weight Gain	QTc Prolongation	Sexual Dysfunction	Sedation
Aripiprazole	Neutral - Low risk	Neutral - Low risk	Neutral - Low risk	Neutral - Low risk	Neutral - Low risk	Neutral - Low risk
Olanzapine	Neutral - Low risk	High risk	High risk	Neutral - Low risk	Neutral - Low risk	Moderate risk
Quetiapine	Neutral - Low risk	Moderate risk	Moderate risk	Neutral - Low risk	Neutral - Low risk	High risk
Risperidone	Moderate risk	High risk	Moderate risk	Neutral - Low risk	Moderate risk	Neutral - Low risk
Ziprasidone	Neutral - Low risk	Neutral - Low risk	Neutral - Low risk	Moderate risk	Neutral - Low risk	Neutral - Low risk

EPS: extrapyramidal side effects



Neutral - Low risk



Moderate risk



High risk

Harrigan EP et al. J Clin Psychopharmacol. 2004;24(1):62-69.

Kim B et al. J Affect Disord. 2008;105(1-3):45-52.

Olfson M, et al. Am J Psychiatry. 2006;163(10):1821-1825.

Keck PE et al. J Clin Psychiatry. 2006;67(4):626-637.

Miller D et al. J Clin Psychiatry. 2001;62(12):975-980.

Yatham LN et al. Bipolar Disord. 2009;11(3):225-255.

EFFECT: Monitoring the response

Parkinson's-Like Symptoms

- Tremor
- Akinesia
- Akathisia
- Rigidity (cogwheel)
- Drooling
- Pisa Sign
- Rabbit Sign
- Gait disturbance

EFFECT: Monitoring the response

Should the Parkinson's - like symptoms be treated with medication ?

Anticholinergics such as benztropine NOT recommended in the elderly may worsen cognition in addition can cause adverse effects such as dry mouth, constipation and urinary retention

Levodopa (e.g. sinemet) is for Parkinson's disease NOT for drug-induced symptoms

EFFECT: Monitoring the response

Newer Antipsychotics: Effect

DASH

Dizziness – Agitation - Somnolence - Hypotension

Olanzapine (anticholinergic)	may cause weight gain, diabetic dyscontrol
Risperidone	may cause EPS at higher doses
Quetiapine	watch for sedation

EFFECT: Monitoring the response

Cognitive Effects of Antipsychotics

- Atypical antipsychotics associated with a MMSE score -2.4 over 36 weeks compared to placebo¹
 - Equivalent to approximately 1 year additional decline
- MMSE -1 point over 8 – 12 week trials²
 - Often LTC population with low MMSE at baseline

1. Vigen, Am J Psychiatry, 2011

2. Schneider, Am J Geriatr Psychiatry

EFFECT: Monitoring the response

Serious Adverse Events

- Mortality: OR=1.6, absolute risk ~1%^{1,2}
 - Number needed to harm: 100
 - Infections, cardiovascular events
- Stroke: RR=2.7, absolute risk ~1%^{2,3}
- Any serious adverse events within 30 days ⁴
 - Atypical: 13.9% (OR: 3.5, 3.1 – 4.1)
 - Typical: 16% (OR=4.2, 95% CI: 3.7 – 4.8)
 - No antipsychotic: 4.4%

1. Schneider, JAMA, 2005

2. Schneider, Am J Geriatr Psychiatry, 2006

3. Herrmann, CNS Drugs, 2005

4. Rochon, Arch Intern Med, 2008

Discontinuing Antipsychotics

- A large proportion of currently stable individuals on antipsychotics can have antipsychotics safely withdrawn^{1,2}
 - Withdrawal associated with 30% increase risk of behavioral worsening compared to placebo ^{1,2}
- Predictors of successful discontinuation:
 - Less severe NPS at initiation of treatment ²
 - Lower dose of antipsychotic required to treat NP

1. Van Reekum, Int Psychogeriatr 2002

2. Ruths, Int J Geriatr Psychiatry, 2008

Medication Use –General Guidelines

Good source of information BPSD algorithm

www.bcbpsd.ca

- Start with a low dose
- Do not titrate too quickly if no response
- Use lowest effective dose
- Monitor and document behaviors
- Reassess need to continue or taper every 3 months

Tapering resident off antipsychotics

- Begin slowly and monitor response
- Start with one or two residents
- Discontinue unused PRNs
- Taper medications for residents without behaviours
- Taper/stop medications prescribed for behaviours unlikely to respond to medication
- Taper/stop medications on admission if used for a resolved delirium/psychosis

Resources

- No evidence that one approach is better than another.
- Consider a slower taper in those with severe baseline symptoms.
- Best done in combination with non-pharmacologic strategies.

Deprescribing.org

www.ChoosingWiselyCanada.org

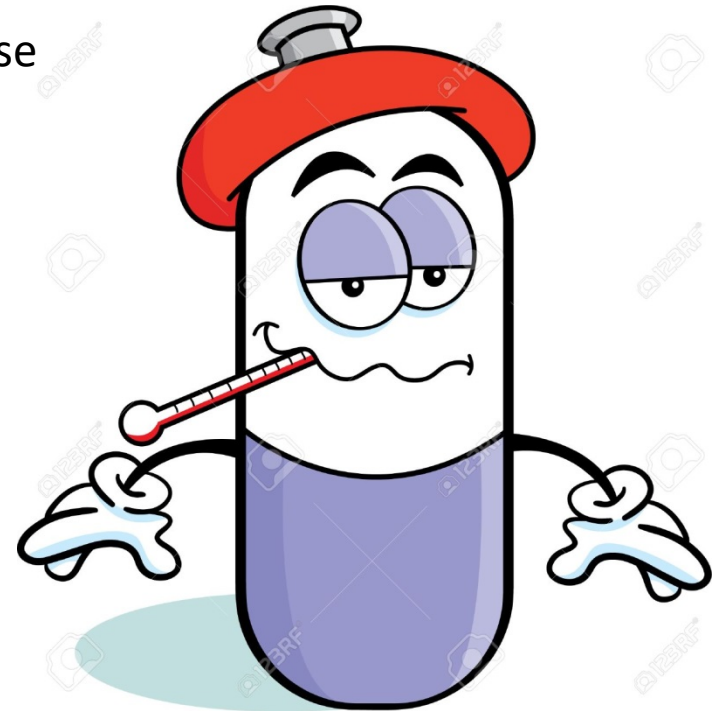
<http://medstopper.com>

- If used daily for 3 to 4 weeks reduce dose by 25% every week and monitor symptoms
- If withdrawal occurs or intolerable symptoms go back to previously tolerated dose (usually 1 to 3 days)
- Once symptoms resolve try again with a more gradual taper
- Discontinuation rate must be balanced with the response of the resident

Possible Symptoms when Stopping or Tapering

- Agitation
- Insomnia
- Nausea/vomiting
- Rebound psychosis

Use lowest effective dose



Summary



- Always consider other alternatives first
- Use only when clinically indicated
- Start low and go slow when starting/stopping medication
- Reduce/stop as quickly as possible when behaviours resolve
- Involve the care team and family in decisions

References

1. www.ChoosingWiselyCanada.org
2. Alberta Health Services- Appropriate use of Antipsychotics in Dementia
3. Deprescribing.org- antipsychotic (AP) Deprescribing Algorithm
4. Remedy's Rx – Medications used in Managing Behaviors in the Elderly