Beyond Cognitive Enhancers: Practical Tips to Optimize Medications for Persons with Dementia in Primary Care

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September 2019
Objectives

1. Describe ways to detect and manage medication non-adherence

2. Discuss common concerns with medication use in persons with dementia

3. Describe ways to optimize use of appropriate medications and minimize use of problematic medications in persons with dementia
   a. De-prescribe medications with potential cognitive adverse effects
   b. Review appropriate targets for hypertension and glycemic control
   c. Ensure appropriate monitoring of persons on cognitive enhancers
Older Adults and Medications

- Among persons age 75 and older:
  - 74.2% use ≥ 1 prescription drug
  - 32.5% use ≥ 3 prescription drugs


- More than 1 in 9 ED visits are due to drug-related adverse events


- Persons age 65 and older are 6.8 times as likely as younger persons to have adverse drug events requiring hospitalization

  Budnitz DS, et al.  JAMA 2006

- 2016 systematic review:
  - Cognitively impaired older adults are at particularly high risk of adverse drug events,
  - Prevalence of adverse drug events ranged from 4.8 to 37%

110 MINT Memory Clinic sites, serving 1/5 of Ontario

- 240+ family physicians
- 55+ specialists
- 750+ nurses and interprofessional healthcare providers
- 200+ community agencies (i.e. Alzheimer’s Society)
Considerations in Medication Management for Cognitively-Impaired Older Adults

1. Is there medication adherence?

2. If the person is taking cognition-enhancing medications for dementia, is this being appropriately monitored?

3. If the person is taking medications for hypertension, are treatment targets appropriate based on functional blood pressure? Is orthostatic hypotension a concern?

4. If the person is taking medications for diabetes mellitus, are treatment targets appropriate? Is hypoglycaemia a concern?

5. Can medications with potential cognitive adverse effects be minimized? These include:
   i. Highly anticholinergic drugs
   ii. Benzodiazepines and nonbenzodiazepine hypnotics
   iii. Antipsychotics
   iv. Opioids
Optimizing medications in older adults with cognitive impairment

Considerations for primary care clinicians

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Abstract

Objective To provide primary care physicians with an approach to medication optimization in older adults with cognitive impairment.

Sources of information The approach is based on an accredited memory clinic training program developed by the Centre for Family Medicine Primary Care Collaborative Memory Clinic.

Main message Dementia increases the risk of medication-related adverse events and adds to the complexity and challenge of providing optimal care for these older adults. Considerations include medication adherence, appropriate therapeutic targets for comorbid conditions, minimized use of medications with potentially adverse cognitive effects, and rational use and monitoring of cognition-enhancing drugs. Medication management plans must be individualized and based on goals of care.

Conclusion Primary care physicians must consider many factors in optimizing medications for those with cognitive impairment.
Medication Non-adherence in Persons with Dementia

- 2017 systematic review: poor adherence to medication regimens in 10.7%-38% of cognitively-impaired persons and 17%-100% with Alzheimer’s dementia

- 2018 systematic review, 18 studies of older patients with dementia: “Medication adherence ranged from 17% to 42%”

- Dementia can affect ability to adhere to complex dosing regimens

- Lower performance on cognitive screening tests associated with difficulty using medication devices
  - MMSE < 24 or inability to copy intersecting pentagons → difficulty using MDI or Turbuhalor device
  - Impaired clock draw → difficulty self-administering insulin

Performance on cognitive screening tests alone cannot be used to determine inability to safely manage medications

Self-report prone to over-estimation

Helpful information may be available from knowledgeable caregiver informants
Intentional and unintentional medication non-adherence
- Unintentional medication non-adherence
  - Cognition, physical limitations, medication complexity

Cognitive capacity results in both over-adherence and under-adherence
- Forgetting
- Dose omission
- Overconsumption by persons on a once-daily dose schedule
- Misunderstanding instructions
- Calculating duration

Assessing Medication Management Capacity

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Assessing Medication Management Capacity: Factors to Consider

Complexity

- Complexity in medication:
  - Number of medications
  - Number of doses
  - Number of actions required to take the medication
  - Change in prescribed drug regimen

Physical Ability

- Vision
  - Reading labels

- Manual dexterity
  - Opening medication containers, childproof most difficult
  - Poor technique with inhalers, injection
  - Compliance packaging – difficulty opening packs


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Assessing Medication Management Capacity

- **Tools (some examples)**
  - Drug Regimen Unassisted Grading Scale (DRUGS)
  - Medication Management Ability Assessment (MMAA)
  - Self Administration Medication Tool (SAM)

- **Strategies**
  - Request all medications be brought: Rx, OTC, vitamins, NHPs
  - Examine bottles, packages, count pills
  - Questions to ask patient/caregiver
    - What, when, how
    - Routine in taking medications
    - Caregiver assistance; caregiver cognition
  - Call pharmacy
    - Automated refills?
    - Pick up on time?
  - Assessment at home
    - Community pharmacist – review medications in pharmacy?
    - Occupational therapist – Home functional abilities assessment

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Strategies to Improve Adherence by Improving Medication Management Capacity

- **Medication Procurement**
  - Refill reminders and pharmacy delivery

- **Physical Ability**
  - Larger labels
  - Color coded bottles
  - Non-childproof containers
  - Compliance packaging
  - Other formulations

- **Complexity**
  - Eliminate inappropriate, unnecessary medications, NHPs, OTCs
  - Simplify regimen – all meds once daily if possible

- **Cognitive Capacity**
  - Memory cues: tailor to patient lifestyle
  - Medication placement: easy to retrieve; visible
  - Medication time: associate with daily activity; transfer single meds to other times, if possible
  - Reminders from caregivers
  - Written instructions; medication calendars
  - Check-off medication list
  - Compliance packaging
  - Automated electronic dispensing devices and real-time monitoring


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Cognitive-Enhancing Drugs

- Reassess regularly for benefit and adverse effects
- Monitor for adverse effects such as bradycardia, syncope, weight loss
- Decisions to continue or discontinue treatment should be individualized and based on goals of care


Stop pharmacotherapy if...

- Patient and/or proxy decide to stop
- Patient is non-adherent or unreliable with medication
- No response to medication
- Intolerable side effects
- Overall condition is deemed palliative
- Dementia has progressed to the point where there is no significant benefit from continued therapy

CHOLINESTERASE INHIBITORS

KEY POINTS

- Efficacy of cholinesterase inhibitors is modest.
- It is unclear whether improvements shown in trials using objective scoring systems would translate into changes for a patient's daily care and supervision requirements.
- It is unclear whether cessation of a cholinesterase inhibitor results in a clinically significant decline in cognition or other dementia symptoms.
- Individualised decisions about discontinuing cholinesterase inhibitors should be made rather than being based on single factors such as MMSE score.
- Patients who have major changes in their life circumstances, such as significant deterioration of health or nursing home placement, should have their cholinesterase inhibitor use reviewed.
- Patients who have serious side effects consistent with use of cholinesterase inhibitors should trial cessation of the agent.

CONTEXT

This guide considers the use of cholinesterase inhibitors to improve cognitive function in people with Alzheimer's disease.

RECOMMENDED DEPREScribing STRATEGY

See page 2 for Deprescribing Algorithm.

BACKGROUND

Cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) are prescribed to improve cognitive function in patients with Alzheimer’s disease, a condition that is expected to triple in prevalence by 2050. Approximately 30% of Australians over 65 had a diagnosis of dementia in 2015 and in the same year, over 50% of patients in permanent residential care had a diagnosis of dementia.

EFFICACY

By inhibiting the synaptic metabolism of acetylcholine, reversible cholinesterase inhibitors enhance cortical cholinergic neurotransmission, intended to improve cognition and delay the effects of Alzheimer's disease.

The efficacy of the cholinesterase inhibitors was reviewed and analysed by Tan et al in 2014. They broadened the spectrum of outcome measures and sought to determine whether there were benefits in cognitive, behavioural or functional impairment in different stages of severity of Alzheimer’s disease.

COGNITIVE FUNCTION

Tan et al reviewed 12 studies of cholinesterase inhibitors (donepezil 6 studies, galantamine 2 studies, rivastigmine 3 studies). All studies evaluated patients with mild to moderate dementia with a mean age of >65 years. Two-thirds of the participants were female. All trials used the Alzheimer’s Disease Assessment Scale-Cognition (ADAS-Cog) to assess cognitive outcomes over 24-week periods and baseline mini mental state examination (MMSE) varied from 10-24. A change in the ADAS-Cog, if a units or more is considered clinically relevant in terms of significant improvement or deterioration in cognition.


Deprescribing Clinical Reference Group
Tenni P, Dunbabin D
The main factors to consider in relation to cholinesterase use are the level of clinically meaningful response achieved and any side effects that may be present.

Clinically meaningful response to treatment is demonstrated in the following areas:

- Patient's quality of life including but not limited to level of independence and happiness;
- Patient's cognitive function including but not limited to memory, recognition and interest in environment;
- Patient's behavioural symptoms, including but not limited to hallucination, delusions, anxiety, marked agitation or associated aggressive behaviour.

Amongst dementia experts, there is a general reluctance to rely on any single measure of cognition, function and/or behaviour (in particular the MMSE) as a guide to efficacy, or to aid in deprescribing decisions.31
Ensure highly anticholinergic drugs are not concomitantly prescribed with cholinesterase inhibitors

- Mechanistically in pharmacologic opposition, potentially reducing effectiveness of one or both drugs

- 10.6% of nursing home residents were prescribed both an AchEI and either oxybutynin or tolteradine → 50% great rate of decline in Activities of Daily Living function as compared to treatment with AchEI alone
  - N=3,536, nursing home residents in Indiana, aged 65+, prescribed an AchEI between 2003-2004
  - Prospective cohort study

Several large cross-sectional studies have demonstrated better cognitive functioning associated with higher SBP and DPB in older adults

May be reverse causality – dementia onset is associated with reduced BP, possibly related to neurodegeneration

There is increasing awareness that overtreatment of hypertension may negatively affect cognition in cognitively-impaired older adults
In adults ≥ age 60:

- Initiate treatment if SBP persistently ≥ 150 mmHg. Aim for SBP <150 (strong recommendation)

- If history of stroke or TIA or at high cardiovascular risk, aim for SBP <140 (weak recommendation)
II. Indications for drug therapy for adults with hypertension without compelling indications for specific agents

Guidelines

1. Antihypertensive therapy should be prescribed for average DBP measurements of ≥ 100 mm Hg (Grade A) or average SBP measurements of ≥ 160 mm Hg (Grade A) in patients without macrovascular target organ damage or other cardiovascular risk factors.

2. Antihypertensive therapy should be strongly considered for average DBP readings ≥ 90 mm Hg (Grade A) or for average SBP readings ≥ 140 mm Hg (Grade B for 140-160 mm Hg; Grade A for > 160 mm Hg) in the presence of macrovascular target organ damage or other independent cardiovascular risk factors.

V. Goals of therapy for adults with hypertension without compelling indications for specific agents

Guidelines

1. The SBP treatment goal is a pressure level of < 140 mm Hg (Grade C). The DBP treatment goal is a pressure level of < 90 mm Hg (Grade A).

Guidelines

1. Persons with diabetes mellitus should be treated to attain SBP of < 130 mm Hg (Grade C) and DBP of < 80 mm Hg (Grade A; these target BP levels are the same as the BP treatment thresholds
Objectives:

- to determine if BP targets ≤ 135/85 mmHG are associated with reduction in mortality and morbidity as compared to BP targets ≤ 140-160/90-100 mmHG in persons with HT and history of CVD (MI, angina, stroke, PVD)
- Systematic review included six RCTs, n=9484, mean follow-up 3.7 yrs

Main results:

- No differences in total mortality, cardiovascular mortality, or serious adverse events or cardiovascular events (including MI, stroke, sudden death, hospitalization, or death from HF)

Conclusions:

- “The best evidence available at this time from randomized controlled trials does not support blood pressure targets < 140 to 160/90 to 100mmHG in people with hypertension and established cardiovascular disease (myocardial infarction, stroke, chronic peripheral vascular occlusive disease or angina pectoris).”
- “Predefined subgroup analyses in older people, in those with diabetes, or based on participant sex did not suggest any differences in these conclusions.”
8.8. Hypertension in older patients (age ≥ 65 years): “Treated SBP values of <130 mmHG should be avoided.”

Williams, et al. Eur Heart J 2018
Orthostatic Hypotension

- Orthostatic hypotension: drop in SBP > 20mm Hg or drop in DBP > 10mm Hg with 3 minutes of standing
  
  Consensus statement, American Autonomic Society and American Academy of Neurology 1996

- Orthostatic hypotension has been associated with worsened cognitive functioning


“Overall, evidence from large population-based cohorts suggests that OH increased the risk of dementia by up to ~50% in the general population”

Robertson AD, et al. Neuropsychiatr Dis Treat 2019
Process for Deprescribing Antihypertensives

- If on multiple antihypertensives, review indication for each medication (remember: some may be treating more than one indication such as secondary prevention of CVD, AF, CHF, renal)
- Start with the ones that have a single indication OR the one that is causing an adverse drug event
- Taper one antihypertensive at a time
  - Decrease dose by 25% every month
  - Abrupt withdrawal of beta blockers increases risk of rebound hypertension, tachycardia, arrhythmia, angina
Medications Commonly Implicated in Inducing Orthostatic Hypotension

- Alpha adrenergic blockers
  - Terazosin, doxazosin, prazosin, tamsulosin
- Beta-blockers
  - Metoprolol, atenolol, etc
- Calcium channel blockers
  - Verapamil, diltiazem
- Diuretics (both thiazide and loop)
  - Hydrochlorothiazide, indapamide, furosemide
- Antipsychotics
  - Olanzapine, risperidone
- Monoamine oxidase inhibitors
  - Selegiline, rasagiline
- Narcotics
  - Morphine
- Dopamine pre-cursors and agonists
  - Levodopa, pramipexole, ropinirole
- Phosphodiesterase inhibitors
  - Sildenafil, vardenafil
- Tricyclic antidepressants
  - Amitriptyline, nortriptyline
- Vasodilators
  - Hydralazine, nitrates

Treatment Options

- **Non-pharmacological**
  - If medication is warranted, advise patients to take medication at bedtime
  - Avoid large meals
  - Limit alcohol
  - Maintain hydration (2 – 2.5L of fluid daily) – not in patients with HF
  - Add salt (not in patients with HF)

- **Pharmacological**
  - Midodrine 10mg TID
    - May cause supine hypertension
  - Pyridostigmine 60mg TID
  - Fludrocortisone 0.1mg daily, titrate weekly to 0.3mg daily
    - Volume overload, hypokalemia, headache, weight gain, edema, supine hypertension

References:
Glycemic control

- “In community-dwelling nursing home-eligible individuals with diabetes, HbA1c of 8.0% to 8.9% was associated with better functional outcomes at 2 years than HbA1c of 7.0% to 7.9%”
  - N=367, Mean age 80, 50% on insulin
  - Yau CK, et al. JAGS 2012

- Among older adults with DM without evidence of cognitive impairment at study baseline, clinically significant hypoglycemia was associated with a 2-fold increased risk for developing dementia and NNH of 5.9
  - N=783, Mean age 74, prospective study over 12 years

- 13% - 23% estimated prevalence of dementia or cognitive impairment in persons with diabetes
Glycemic control

In the U.S.

- Insulins and/or oral hypoglycemic agents implicated in ¼ of emergency hospitalizations for adverse drug events in older adults, mainly due to hypoglycemia

- Insulin second only to warfarin as the top two drugs implicated in nearly 1/3 of ED visits due to adverse drug events in older adults

If insulin is required, administration technique and adherence must be closely monitored, focusing on individual therapeutic goals and avoidance of hypoglycemia
“It has been suggested that postprandial glucose are a better predictor of outcome in older people with diabetes than A1C or preprandial glucose values”
<table>
<thead>
<tr>
<th>Measure</th>
<th>ADA</th>
<th>DC</th>
<th>IDF</th>
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<tbody>
<tr>
<td>A1C</td>
<td>Healthy: ≤ 7.5%</td>
<td>Functionally independent: ≤ 7.0%</td>
<td>Functionally independent: 7.0%–7.5%</td>
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<tr>
<td></td>
<td>Complex/Intermediate ≤ 8.0%</td>
<td>Functionally dependent: 7.1–8.0%</td>
<td>Functionally dependent: 7.0%–8.0%</td>
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<tr>
<td></td>
<td>Very Complex/Poor Health: ≤ 8.5%</td>
<td>Frail and/or dementia: 7.1–8.5%</td>
<td>Sub-level frail: &lt; 8.5%</td>
</tr>
<tr>
<td></td>
<td>End of life: A1C measurement not recommended. Avoid symptomatic hyperglycemia and any hypoglycemia.</td>
<td>End of life: avoid symptomatic hyperglycemia</td>
<td></td>
</tr>
<tr>
<td>Blood Pressure mmHg</td>
<td>Healthy: &lt; 140/80</td>
<td>Functionally independent with life expectancy</td>
<td>Functionally independent: &lt; 140/90</td>
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<tr>
<td></td>
<td>≥ 10 years: &lt; 130/80 mmHg</td>
<td>Functionally dependent, orthostasis or limited life expectancy: individualize BP targets</td>
<td>Sub-level frail: &lt; 150/90 mmHg</td>
</tr>
<tr>
<td></td>
<td>Complex/Intermediate ≤ 140/80 mmHg</td>
<td>Functionally dependent: &lt; 140/90 mmHg</td>
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</tr>
<tr>
<td></td>
<td>Very Complex/Poor Health: ≤ 150/90 mmHg</td>
<td>End of life: strict BP control may not be necessary</td>
<td>End of life: avoid symptomatic hyperglycemia</td>
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</tbody>
</table>
Assess potential contributors of hypoglycemia
- Drug interactions
- Recent d/c of drugs that cause hyperglycemia
- Not eating

Options to address hypoglycemia
- Reduce dose of current agents (esp sulfonylureas)
- Stop (esp insulin)
- Switch to another agent with lower risk of hypoglycemia (sulfonylureas to metformin, sitagliptin)

Monitor
- Signs of hyperglycemia over 1 – 2 weeks
- HbA1C for increase
**Benzodiazepines and Nonbenzodiazepine Hypnotics**

- 15% - 20% estimated prevalence of benzodiazepine use in Canadians aged 65 and older
  

- Benzodiazepines can adversely affect memory, attention, and reaction time

- Evidence implicating non-benzodiazepine derivatives is less consistent
  
  Tannenbaum C, et al. Drugs Aging 2012

- Benzodiazepine users have increased occurrence of cognitive deficits

Large population-based and data base studies suggest benzodiazepine use, particularly long-acting and long-term use, is strongly associated with increased risk of developing dementia

- Large US and Canadian database study: “multi-methodological approaches using different methods, algorithms and databases suggest that long-term use of benzodiazepines and long-acting benzodiazepines are strongly associated with an increased risk of dementia”
  

- Prospective cohort study of men seen on 5 occasions over 22 years, n= 1134: those taking benzodiazepines regularly at one or more phases showed a marked increased incidence of dementia (OR 3.50, CI 1.57 to 7.79, p=0.002)
  

- Case-control study, Quebec health insurance program database, n=1796 persons with AD: Benzodiazepine ever use was associated with an increased risk of AD (OR 1.51, CI 1.35 to 1.69); strength of association increased with exposure density and with drug half life
  
  Billoti de Gage S, et al. BJM 2014
2016 systematic review and meta-analysis: 1.78 fold increased risk of developing dementia in older persons who use benzodiazepines for more than 30 days

Fig. 2. ORs and 95% CIs from studies of risk of dementia in patients receiving benzodiazepines.
### Benzodiazepine Withdrawal Strategies

<table>
<thead>
<tr>
<th>Approach</th>
<th>Methods</th>
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<tbody>
<tr>
<td><strong>Abrupt Discontinuation</strong></td>
<td>• Immediate cessation</td>
</tr>
<tr>
<td><strong>Minimal Intervention</strong></td>
<td>• Letter; Self-help booklet&lt;br&gt;• Brief consultation; One-time counseling</td>
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<tr>
<td><strong>Gradual Discontinuation</strong></td>
<td>• Dose-tapering schedules&lt;br&gt;• 10 – 25% every 1 – 2 weeks</td>
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<tr>
<td><strong>Psychotherapy</strong></td>
<td>• Cognitive behavioural therapy</td>
</tr>
<tr>
<td><strong>Gradual Discontinuation + Psychotherapy</strong></td>
<td>• Dose tapering + CBT</td>
</tr>
<tr>
<td><strong>Gradual Discontinuation + Pharmacotherapy</strong></td>
<td>• Dose tapering + Adjuvants (paroxetine, melatonin, SSRI, buspirone, trazodone, valproate, carbamazepine, propranolol, imipramine)</td>
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Strategies for Benzodiazepine Withdrawal

- **Treat underlying disorder** (anxiety, insomnia, seizures) adequately
- **Go slow** (especially if elderly, long-term use)
- If required, **switch to diazepam** (equivalent dose)
- **Decrease daily dose by 25 – 50% per week** initially (may decrease by 10 – 25% for elderly, chronic use and prolonged time frame i.e. every 2 – 4 weeks)
- **Slow down taper further once titrated to 50%** (taper by 10%, over q 2 – 4 weeks based on patient preference)
- To improve rates of cessation, **incorporate CBT**
Benzodiazepine Withdrawal Guidelines

Engaging patients and caregivers

- Patients should understand:
  - The rationale for de-prescribing (associated risks of continued BZRA use, reduced long-term efficacy).
  - Withdrawal symptoms ( insomnia, anxiety) may occur but are usually mild, transient and short-term (days to a few weeks).
  - They are part of the tapering plan, and can control tapering rate and duration.

Tapering doses

- No published evidence exists to suggest switching to long-acting BZRA reduces incidence of withdrawal symptoms or is more effective than tapering shorter-acting BZRA.
- If dosage forms do not allow 25% reduction, consider 50% reductions initially using drug-free days during latter part of tapering, or switch to lorazepam or oxazepam for final taper steps.

Behavioural management

Primary care:
1. Go to bed only when sleepy.
2. Create use bed or bedtimes for anything but sleep or resting.
3. If not asleep within about 30 minutes at the beginning of the night, or after an awakening, exit the bedroom.
4. If not asleep within 20 minutes on returning to bed, repeat #5.
5. Use alarm to awaken at the same time every morning.
6. Do not nap.
7. Avoid caffeine, alcohol after noon.
8. Avoid exercise, nicotine, alcohol, and big meals within 2 hours of bedtime.

Institutional care:
1. Pull-up curtains during the day to obtain bright light exposure.
2. Keep alarm noises to a minimum.
3. Increase daytime activity & discourage daytime sleeping.
4. Reduce number of naps (no more than 30 mins and no naps after 2 p.m).
5. Offer warm, decaff drink, warm milk at night.
6. Restrict food, caffeine, smoking before bedtime.
7. Place the resident toilet before going to bed.
8. Encourage regular bedtimes and rising times.
9. Avoid waking at night to provide direct care.
10. Offer backrub, gentle massage.

Using CBT

- What is cognitive behavioural therapy (CBT)?
  - CBT includes 5-6 educational sessions about sleep, insomnia, stimulus control, sleep restriction, sleep hygiene, relaxation training and support.
- Does it work?
  - CBT has been shown in trials to improve sleep outcomes with sustained long-term benefits.
- Who can provide it?
  - Clinical psychologists usually deliver CBT, however, others can be trained or can provide aspects of CBT education; self-help programs are available.
- How can providers and patients find out about it?
  - Some resources can be found here: http://sleepwise.ca/
Use is associated with deleterious effects on divided attention, reaction time, and reduced performance in tasks requiring attention and vigilance

Higher cumulative use of anticholinergic medications is associated with increased risk of dementia which may persist despite discontinuation of therapy

- 10 year prospective US population-based cohort study, n=3,434 aged 65+
- Those with higher exposure (>1094 days) had significantly increased risk for dementia (HR 1.54, CI 1.21-1.96 for all-cause dementia and HR 1.64, CI 1.24-2.13 for AD) compared to no use
- As examples, persistent increased dementia risk was associated with ≥ 3 years use of oxybutynin 5mg or olanzapine 2.5mg or doxepin 10 mg
“Exposure to several types of strong anticholinergic drugs is associated with an increased risk of dementia. These findings highlight the importance of reducing exposure to anticholinergic drugs in middle-aged and older people.”

- Nested case-control study, England, n=58,769 patients with dementia and 225,574 controls, aged 55+
  - OR for dementia increased from 1.06 (CI 1.03-1.09) in the lowest anticholinergic exposure category to 1.49 (CI 1.44-1.54) in the highest category compared with no anticholinergic drug prescriptions in the 1 to 11 years before the index date.
  - Associations were strongest for anticholinergic antidepressants, bladder antimuscarinics, antipsychotics, and antiepileptic drugs.

“An association between some anticholinergic drugs and future dementia incidence was observed.”

- Nested case-control study, UK, n=40,770 patients with dementia and 283,933 controls, aged 65-99, median drug exposure period 7.1 years
  - Significant association between dementia incidence and any prescription of antidepressant, antiparkinson, or urological drugs with an Anticholinergic Burden Score of 3, seen even for exposures 15-20 years before diagnosis of dementia (OR for different exposures between 1.1 and 1.3)
  - Could be class specific effect

Coupland CAC, et al. JAMA Intern Med 2019

Richardson K, et al. BMJ 2018
Common Drugs with High Anticholinergic Risk

- Antimuscaranics
  - Darifenacin, fesoterodine, oxybutynin, flavoxate, solifenacin, tolterodine, trospium

- Antiparkinsonian medications
  - Benztropine, trihexyphenidyl

- Antipsychotics
  - Chlorpromazine, clozapine, loxapine, olanzapine, perphenazine, thioridazine

- Antispasmodics
  - Tropine, belladonna

- Muscle relaxants
  - Cyclobenzaprine, orphenadrine

- Antiarrhythmics
  - Disopyramide

- Antidepressants
  - Amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, amoxapine, protriptyline, trimipramine, paroxetine

- Antiemetics
  - Prochlorperazine, promethazine

- Antihistamines
  - Brompheniramine, chlorpheniramine, dimenhydrinate, diphenhydramine, doxylamine, hydroxyzine, meclizine, dicyclomine, etc
Management Strategies for Anticholinergic Drugs

- Investigate indication for use
  - Depression
  - Insomnia
  - Behaviour
  - Pain
  - Allergies
  - Parkinson’s disease

- De-prescribe and trial non-pharmacologic strategies
  - Insomnia – sleep hygiene, exercise
  - Behaviour – music therapy

- Replace with safer alternative (low risk of anticholinergic activity) based on indication (examine risk of falls)
  - Depression – other SSRIs, SNRIs
  - Neuropathic pain – SNRI, capsaicin
  - Parkinson disease – dopamine precursors

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Antipsychotic Drugs

- Systematic reviews and meta-analyses suggest modest benefits for use of antipsychotic drugs in the management of psychosis and aggression in persons with dementia.

- Potential harms include increased risk of stroke and mortality.

Maust DT, et al. JAMA Psychiatry 2015
Kales HC, Am J Geriatr Psychiatry 2012

<table>
<thead>
<tr>
<th>Antipsychotics: Potential Benefits</th>
<th>Antipsychotics: Potential Harms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited benefit: modest improvement seldom observed</td>
<td></td>
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<tr>
<td>• effect size: 0.12-0.2</td>
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<tr>
<td>• NNT variable: ~5-14</td>
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<tr>
<td>(i.e. at best, compared to placebo, antipsychotic therapy results in targeted behaviour benefit in 1 out of 5 people treated)</td>
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| Side effects: sedation, falls, postural hypotension, QT prolongation, confusion, EPS (rigidity, stiffness, akinesia), tardive dyskinesia, diabetes, weight gain |
| Stroke: increased risk |
| Death: possible increase |
| Health Canada Advisory noted a 1.6 fold increase in mortality (mostly related to heart failure, sudden death, pneumonia). Some data suggests that there will be 1 extra stroke or death for every ~100 people treated (NNH=100). |

KEY: EPS: extrapyramidal symptoms (Parkinson's-like); NNT: number needed to treat to see one extra benefit; NNH: number needed to treat to see one extra harm
Degree of mortality risk may vary with type of antipsychotic, and risk increases with dose
- Retrospective case control study, Veterans Health Administration data 1998-2009
- n=90,786 patients aged 65+ diagnosed with dementia
- 180 day observation period
- Mortality risk compared using antidepressant group as reference

Maust DT, et al. JAMA Psychiatry 2015
Antipsychotic Drugs

- Aim is to decrease dangerous and aggressive behaviours without oversedation

2015

The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients With Dementia

Statement 14. APA recommends that in the absence of delirium, if nonemergency antipsychotic medication treatment is indicated, haloperidol should not be used as a first-line agent. (1B)

"...data from randomized placebo-controlled trials suggest efficacy for risperidone in treating psychosis and for risperidone, olanzapine, and aripiprazole in treating agitation. There was insufficient information from trials of quetiapine to determine whether it was efficacious in treating either agitation or psychosis, and it appeared to be no better than placebo in treating behavioral or psychological symptoms of dementia overall."


Risperidone, olanzapine and aripiprazole can be used for severe agitation, aggression and psychosis where there is a risk of harm to the patient and/or others. The potential benefit of all antipsychotics must be weighed against the significant risks such as cerebrovascular adverse events and mortality (Grade 2A).
Antipsychotic Drugs

- Antipsychotic drugs are associated with significant cognitive adverse effects
  - “In CATIE-AD atypical antipsychotics were associated with worsening cognitive function at a magnitude consistent with one year’s deterioration compared with placebo”
    
  
  - 2006 Meta-analysis of randomized, placebo-controlled trials of atypical antipsychotics in patients with AD or dementia: “Cognitive test scores worsened with drugs”
    
Withdrawal Strategies: Antipsychotics

Abrupt Discontinuation
- Immediate cessation

Gradual Discontinuation
- Dose tapering schedules
  - 25-50% dose reduction every 1-2 weeks
Strategies for successful withdrawal*

- Trial after 3 months on treatment
- No recent change in dose or frequency
- Ensure problematic BPSD symptoms not demonstrated
- Abrupt d/c – reserve for significant drug interaction or severe adverse effect
  - Go Slow (esp short half-life, long duration of use, higher dose)
    - 25 – 50% dose reduction every 1 – 2 weeks
- Monitor for relapse, withdrawal effects

*Expert opinion and personal experience

Osser D, et al. NaRCAD 2013

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Antipsychotic Deprescribing Algorithm

Figure 1

Antipsychotic (AP) Deprescribing Algorithm

Why is patient taking an antipsychotic?

- Psychosis, aggression, agitation (behavioural and psychological symptoms of dementia - BPSD) treated ≥ 3 months (symptoms controlled, or no response to therapy).
- Primary insomnia treated for any duration or secondary insomnia where underlying comorbidities are managed.
- Schizophrenia
- Schizo-affective disorder
- Bipolar disorder
- Acute delirium
- Tourette's syndrome
- Tic disorders
- Autism
- Less than 3 months duration of psychosis in dementia
- Mental retardation
- Developmental delay
- Obsessive-compulsive disorder
- Alcoholism
- Cocaine abuse
- Parkinson's disease psychosis
- Adjunct for treatment of Major Depressive Disorder

Recommend Deprescribing

Strong Recommendation (from Systematic Review and GRADE approach)

Taper and stop AP (slowly in collaboration with patient and/or caregiver; e.g. 25%-50% dose reduction every 1–2 weeks)

Stop AP
Good practice recommendation

Monitor every 1-2 weeks for duration of tapering

Expected benefits:
- May improve alertness, gait, reduce falls, or extrapyramidal symptoms
- Averse drug withdrawal events (closer monitoring for those with more severe baseline symptoms):
  - Psychosis, aggression, agitation, delusions, hallucinations

If BPSD relapses:
Consider:
- Non-drug approaches (e.g. music therapy, behavioural management strategies)

Restart AP drug:
- Restart AP at lowest dose possible if resurgence of BPSD with re-titration of deprescribing in 3 months
- At least 2 attempts to step should be made

Alternate drugs:
- Consider change to risperidone, olanzapine, or aripiprazole

Continue AP or consult psychiatrist if considering deprescribing

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Cognitive effects can include inattention, concentration difficulties, memory deficits, and executive dysfunction

Opioids are associated with 2 to 3 fold increased risk of delirium

- Highest risk associated with meperidine

Pain may be under-recognized and under-treated in dementia and may exacerbate symptoms of agitation, aggression, and mood
Considerations with Opioid Use in Persons with Dementia

- Accurate assessment of pain is challenging in persons with advanced dementia. Dementia pain scale ratings may be more accurate than verbal report in detecting pain and monitoring response to pain medications.

- If escalating opioids is not associated with improvement in aggressive expressions, then pain may not be underlying the agitation/aggression

- If escalating opioids is not associated with improvement in pain response, consider reducing opioids

- If reducing opioids does not increase pain scale ratings, then pain not be underlying the agitation/aggression
### Pain Assessment in Advanced Dementia (PAINAD) Scale

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Negative Vocalization</strong></td>
<td>None</td>
<td>Occasional moan or groan. Low level speech with a negative or disapproving quality.</td>
<td>Repeated troubled calling out. Loud moaning or groaning. Crying.</td>
<td></td>
</tr>
<tr>
<td><strong>Facial Expression</strong></td>
<td>Smiling or inexpessive</td>
<td>Sad. Frightened. Frown.</td>
<td>Facial grimacing.</td>
<td></td>
</tr>
<tr>
<td><strong>Consolability</strong></td>
<td>No need to console</td>
<td>Distracted or reassured by voice or touch.</td>
<td>Unable to console, distract or reassure.</td>
<td></td>
</tr>
</tbody>
</table>

**Scoring:**

- **1-3** Mild pain  
  Provide comfort measures (i.e., non-pharmacologic approaches such as repositioning or distraction or a mild analgesic such as acetaminophen)

- **4-6** Moderate pain

- **7-10** Moderate to Severe pain  
  Pain that warrants stronger analgesia, such as an opioid, as well as comfort measures

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Suggestions for Managing Opioids

- Investigate indication for opioid
  - Neuropathic pain
  - Nociceptive pain
- Investigate effectiveness of non-opioid medications trialed so far
  - Adequate dose?
  - Adequate trial?
  - Risk versus benefit
- Neuropathic/mixed pain
  - SNRI, anticonvulsants (gabapentin, pregabalin: use judiciously)
- Nociceptive pain
  - Acetaminophen prescribed round the clock (not at max dose)
  - Topical agents (lidocaine, capsaicin, topical NSAIDs)
- Determine total daily morphine equivalent dose across all formulations; taper slowly
- Consider cross-taper
- Avoid/minimize
  - TCAs
  - Cyclobenzaprine, methocarbamol, baclofen
  - NSAIDs

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Ensure medication adherence

Ensure cognition-enhancing medications for dementia are being appropriately monitored

Consider appropriate hypertension treatment targets based on functional blood pressure. Check for orthostatic hypotension.

For those with diabetes, consider appropriate glycemic targets. Avoid hypoglycemia

Minimize medications with potential cognitive adverse effects:
  i. Highly anticholinergic drugs
  ii. Benzodiazepines and nonbenzodiazepine hypnotics
  iii. Antipsychotics
  iv. Opioids