DEMENTIA
BRINGING EVIDENCE & EXPERIENCE TO DRUG THERAPY DECISION POINTS
October 2014

INSIDE
Pg 3: Cholinesterase Inhibitors (ChEI) in Dementia
Pg 7: Geri-RxFiles - Dementia & Cognitive Impairment
Pg 12: Geri-RxFiles – Anticholinergics Reference List
Pg 13: Geri-RxFiles – Dementia: Behavioural & Psychological Symptoms (BPSD)

RESOURCES & LINKS (FOR FAMILY):
⇒ Alzheimer’s Society: http://www.alzheimer.ca/en
⇒ FirstLink-SK: http://www.alzheimer.ca/en/sk/We-can-help/First-link-start

REAL-LIFE CHALLENGES Clinician quotes
⇒ I recommend trying a ChEI, but they really don’t work.
⇒ It’s not easy to explain benefits & harms to patients & families.
⇒ Current guidelines recommend a ChEI trial, but clinicians seem divided on this.
⇒ It’s hard not to overestimate or underestimate concerns re: medications in dementia. A balanced approach eludes us!

NEW AT RXFILES
& Geri-RxFiles – May 2014.

Impaired Cognition, Function & Behaviours: Drug Related Considerations

Initial Assessment
⇒ Assess for reversible causes
  • drug causes e.g. anticholinergic load
  • B12 deficiency
⇒ Plan for future uncertainties
  • advanced care directives
  • power of attorney in place

Upon Early Diagnosis of Dementia
⇒ Note the role & value of non-drug measures (see pg 6) on quality of life
⇒ Decide whether a trial of cholinesterase inhibitors (ChEIs) is indicated
⇒ Determine whether a trial of a ChEI is desirable to the patient/family

<table>
<thead>
<tr>
<th>Cholinesterase Inhibitors (ChEI) for Alzheimer's Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefits/Advantages</td>
</tr>
<tr>
<td>- Stabilizing or slowing progression of</td>
</tr>
<tr>
<td>Alzheimer’s dementia in terms of</td>
</tr>
<tr>
<td>cognitive testing (modest)</td>
</tr>
<tr>
<td>- marked improvement, uncommon, NNT=42</td>
</tr>
<tr>
<td>- at least minimal improvement, NNT=12</td>
</tr>
<tr>
<td>- cognitive stabilization, NNT=7</td>
</tr>
<tr>
<td>(Note: benefit was not noticeable to the patients taking the ChEI in trials)</td>
</tr>
<tr>
<td>- Stimulating, sometimes resulting in less apathy</td>
</tr>
</tbody>
</table>

Limitations: Evidence fails to show functional improvement or preservation of independence. Studies have not involved typical patients; harms likely more frequent.

What to expect from not trying ChEI but initiating non-drug measures?

| Benefits/Advantages                                      | Harms/Disadvantages                        |
|------------------------------------------------------------|
| - Expect improvement in quality of life                    | - May miss out on the chance that there may be some improvement that is clinically relevant for a period of time.
| - Avoid the side effects of the ChEI                      |                                                      |
| - Results in one less drug & drug cost                     |                                                      |
| - Note: rate of cognitive stabilization for placebo in trials was 51% (vs 66% for ChEI) |                                                      |

⇒ Provide a realistic picture of potential benefits, harms & costs of trialing versus not trialing a ChEI in the context of patient values. Discuss with patient and/or family.
⇒ Consider a trial of a ChEI (e.g. donepezil) when suitable and desired.
⇒ Monitor & reassess! The decision to continue depends on realizing adequate benefit and tolerability.
⇒ Note: ChEIs less likely to be effective in non-Alzheimer’s dementias.
Memantine is an alternative option with its own advantages & disadvantages.

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Behavioural & Psychological Symptoms of Dementia (BPSD) Management

⇒ Non-drug strategies will often be the most useful!
⇒ Pharmacological management has a role in addressing certain symptoms, especially when patient or caregiver safety is threatened.
⇒ When medications are used (e.g. risperidone, quetiapine for aggression, especially when severe and there is risk of harm to patient or caregiver):
  • trial, with caution, the most appropriate medication for the symptom
  • monitor for evidence of relative benefit vs harm
  • reassess for possible taper & discontinuation every 3 months
⇒ See Pg 13 for a detailed discussion of BPSD

**Behind the Scenes at RxFiles**

**RxFiles hosts the... National Academic Detailing Conference: Focus on Dementia & Polypharmacy.**

Continuing Professional Development, Schulich School of Medicine & Dentistry, Western University, in collaboration with RxFiles Academic Detailing Program and the Canadian Academic Detailing Collaboration (CADC) hosted a 2.5 day National Academic Detailing Conference in September, 2014. The conference was jointly branded by the three organizations.

**Hearing from family & staff...**
The conference started off at a long-term care (LTC) home in Saskatoon where we listened to family members, LTC staff, and a LTC family physician tell their stories and experiences in a panel discussion format.

**Joel Lamoure entertains & informs...**
Joel shared the results of an award winning project by the Schulich School of Medicine & Dentistry, Western University, London, ON. The conference was made possible through a grant from Schullich, for which we were all very grateful.

**Our Guest Facilitator, Frank May**
Frank May comes from Australia, and fortunately for us, he is often passing through North America and able to slip in a visit to help out with conferences and workshops like ours. His important contribution to the academic detailing community in Canada was recognized by the CADC during the conference.

**Lots of input & discussion...**
The conference involved 11 family physicians, 2 geriatric psychiatrists, & a host of others from RxFiles and the CADC community from BC, MB, ON and NS. *Thanks to everyone!!!*

**And of course everyone had a tiny bit of time to just be themselves.**

ACKNOWLEDGMENTS: We would like to thank those who contributed to our conference &/or the development & review of this newsletter including Dr. L. Thorpe, Dr. M. Davidson, Dr. M. McCord, Dr. B. Martens, Dr. J. Alport, Dr. V. van der Merwe, Dr. N. Olsen, Dr. K. Ruelens, Dr. S. Bogdien, Dr. B. Schuster, D. Bunka, A. Crawley, the families & staff at Sunnyside, & the rest of the RxFiles team. L. Regier, J. Barnham
Cholinesterase Inhibitors (ChEI) in Dementia

----- HIGHLIGHTS -----

✓ Cholinesterase inhibitors (ChEI) may offer a modest benefit in stabilizing or slowing progression of Alzheimer’s dementia. This benefit often competes with significantly poor tolerability (e.g. gastrointestinal: diarrhea, nausea; bradyarrhythmias, risk of falling, urinary incontinence, sometimes behavioural disturbance) & questionable clinical usefulness.

✓ A patient-centred approach is essential when considering trial of a ChEI. Offering a balanced description of benefits, harms & realistic expectations will help patients and families to make decisions on trialing, continuing vs tapering, or discontinuing therapy. Employing non-drug measures without a ChEI will often be preferred.

✓ Avoid or limit the use of anticholinergics in combination with a ChEI, as use may diminish or negate benefits of the ChEI. When urinary incontinence and dementia co-exist, a decision must often be made regarding which one to treat.

What are the indications for cholinesterase inhibitors?

Cholinesterase inhibitors (donepezil, galantamine, rivastigmine, and galantamine) are medications designed to prevent the breakdown of the neurotransmitter acetylcholine. Insufficient levels of acetylcholine are thought to be a factor in the cause and progression of Alzheimer’s disease. While originally designed and marketed for mild to moderate Alzheimer’s disease (MMSE 10-26), ChEIs have now been studied in multiple types of dementia. It is important to remember that prescribing for dementia beyond Alzheimer’s disease is usually off-label. Such use may not meet the indication criteria required for drug plan coverage. Of further importance is that differentiating between the various types of dementia is challenging; many patients present with a mixed pathogenesis. Anecdotally, ChEIs may be stimulating in some patients resulting in either a benefit (less apathy), or harm (more agitation and behaviour disturbance).

Table 1: Cholinesterase Inhibitors: Potential Role Based On Evidence for Benefits vs Harms

| Alzheimer’s Disease (AD) | Associated with brain changes referred to as plaques and tangles. Initial forgetfulness progresses to profound memory loss. Patients eventually require full-time care. | Many RCTs n = 161-979 show a modest benefit. All three ChEIs approved for treatment of mild-moderate AD dementia; donepezil approved for severe AD dementia.† | Meta-analysis - trials of 12-54 weeks²
NNT=7 stability or improvement (95%CI 6-9)
NNT=12 minimal improvement (95%CI 9-16)
NNT=42 marked improvement (95%CI 26-114)
NNH = 12 any adverse effect (95%CI 10-18) |
---|---|---|---|
| Parkinson’s Disease (PD) | Parkinson’s disease frequently leads to dementia. May present as Alzheimer’s type or Lewy Body type. | RCTs n = 14-550 with rivastigmine & donepezil have shown small benefits of clinically questionable significance. Rivastigmine approved for mild-moderate PD dementia. Can exacerbate parkinsonism.⁶ | Rivastigmine & donepezil can be expected to increase MMSE by ~1 point over 10-24 weeks versus placebo.² |
| Vascular Dementia (VaD) | Dementia occurs due to a loss of blood flow to the brain. Executive dysfunction with sparing of memory is typical. | RCTs n = 382-978 with donepezil, galantamine, & rivastigmine have shown small benefits of clinically questionable significance.³⁴ | Non-significant for stability or improvement vs placebo; positive change of +2 points over 24-26 weeks in the ADAS-Cog test vs placebo.⁴ |
| Lewy Body Dementia (LBD) | Shares many symptoms in common with Parkinson’s disease. Characterized by visual hallucinations; falls are common. | Rivastigmine RCT n = 120 showed no benefit in cognition over 20 weeks vs placebo. ⁵² | Cholinesterase inhibitors unlikely to be effective for improving cognition; may be considered for hallucinations.²⁵, Expert Opinion |
| Frontotemporal Dementia (FTD) | Strong genetic pattern of inheritance; begins earlier in life than AD and rapidly progresses. Changes occur first to speech and personality. | FTD does not appear to be associated with acetylcholine.⁷ ChEI therapy has not been evaluated in a placebo-controlled trial. Some evidence suggests ChEIs may actually worsen behaviour.⁵⁶ | Cholinesterase inhibitors unlikely to be effective. |

Note: given that patients in trials were less severe with fewer co-morbidities, some expect less benefit, but more harm in real life.

Is ChEI effectiveness clinically significant?

Given the modest potential for benefit, a decision to treat means carefully weighing the potential harms.

- Consider offering most patients with a diagnosis of mild to moderate Alzheimer’s disease a cholinesterase inhibitor trial.¹⁻³⁻¹³⁴CDT04 Patient and family opinion, once adequately informed, is highly important.
- Consider the stage of dementia the medications are being started in. While these drugs have been studied in severe dementia, keeping a MMSE stable at 7 may not be valuable. Achieving stabilization or improvement of MMSE from 16 to 17 on the other hand may be significant to some patients or families.
- Consider the premise of non-responders and responders. There is evidence that some patients (~10%) will experience a significant effect after starting a ChEI (perhaps a 4 point increase in MMSE).³ Unfortunately, patient response cannot be predicted - other patients (~10%) will experience a rapid decline in cognitive function. (Placebo has benefit in trials!)

“Once you have seen one dementia patient, you have seen one dementia patient.”²
What are the cost considerations?
- Generic availability has made all ChEIs more affordable, with a monthly cost around $70 per month. (The cost of these drugs was previously around ~$200/month.)
- Despite high hopes, ChEIs have not been shown to reduce health system costs through decreasing hospitalizations or nursing home admissions. (AD2000)\(^{10,12}\)

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**To initially qualify for Saskatchewan EDS coverage, patients must:**

<table>
<thead>
<tr>
<th>MMSE Dementia Scoring</th>
<th>0-9</th>
<th>10-19</th>
<th>20-26</th>
<th>27-30</th>
</tr>
</thead>
<tbody>
<tr>
<td>severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mild</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| note that language barriers & level of education must be considered when scoring as they may decrease the score. |

1. Have a diagnosis of (probable) Alzheimer’s disease
2. Have a MMSE score of 10-26*
3. Have completed a Functional Activities Questionnaire (FAQ)**
4. Discontinue all anticholinergic drugs***

* A copy of the MMSE & instructions may be found at: http://www.albertahealthservices.ca/hp/if-hp-ltc-pharm-cholinesterase-inhibitor-self-study-module.pdf

** A copy of the FAQ may be found at: http://consultgerin.org/uploads/File/trythis/try_this_d13.pdf


Assessment of MMSE and FAQ must be completed by prescribing physician or nurse practitioner; documentation to be signed and submitted may be found here: http://www.health.gov.sk.ca/form-he599

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**To continue to qualify for Saskatchewan EDS coverage, patients must:**

1. After first assessment (3 months), demonstrate improvement of +2 on MMSE or -1 on FAQ.
2. After all future assessments (every six months), not have both a >2 point reduction in MMSE and a ≥1 point increase in FAQ.
3. Remain above MMSE of 10 at all times.
4. Continue to not use drugs listed with substantial anticholinergic effect.

Patients with MMSE improvement to >26 continue to qualify for coverage.

Reassessment of MMSE and FAQ may be completed by any licensed health care professional; final documentation must be signed and submitted by prescribing physician or nurse practitioner (http://www.health.gov.sk.ca/form-he599)

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### Table 2: Typical Dose and Cost of Cognitive Therapy Medications

<table>
<thead>
<tr>
<th>Cholinesterase Inhibitors</th>
<th>SK/NIH coverage?</th>
<th>Dose</th>
<th>Cost/month</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donepezil</strong></td>
<td>ARICEPT, g</td>
<td>EDS ≥ / Prior approval re</td>
<td>Initial: 5mg po daily</td>
</tr>
<tr>
<td><strong>Galantamine</strong></td>
<td>REMINYL, g</td>
<td>EDS ≥ / Prior approval re</td>
<td>Initial: 8mg ER po daily</td>
</tr>
<tr>
<td><strong>Rivastigmine</strong></td>
<td>EXELON, g</td>
<td>EDS ≥ / Prior approval re</td>
<td>Initial: 1.5mg po BID</td>
</tr>
<tr>
<td><strong>Miocholine</strong></td>
<td>EBIKA, g</td>
<td>NO: X/°</td>
<td>Initial: 5mg po daily</td>
</tr>
</tbody>
</table>

### Table 3: Cholinesterase Inhibitor Drug Interactions

<table>
<thead>
<tr>
<th>Pharmacodynamic</th>
<th>Drug</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antipsychotics</strong></td>
<td>donepezil</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Anticholinergics</strong></td>
<td>galantamine</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Beta-blockers</strong></td>
<td>rivastigmine</td>
<td>✔</td>
</tr>
</tbody>
</table>

**Pharmacokinetic**

<table>
<thead>
<tr>
<th>CYP3A4 inhibitors (e.g. erythromycin, clarithromycin, fluconazole, ketoconazole)</th>
<th>✔</th>
<th>✔</th>
<th>✔</th>
<th>↓ ChEI metabolism and ↑ levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6 inhibitors (e.g. fluoxetine, paroxetine, quinidine)</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>↑ ChEI metabolism and ↓ levels</td>
</tr>
<tr>
<td>CYP inducers (e.g. rifampin, carbamazepine)</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Nicotine / Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What about patients taking anticholinergics for incontinence?

Anticholinergic incontinence medications can impair cognition/cognitive performance.

- In patients with dementia, anticholinergic medications should be avoided.\(^{30}\)
- In non-demented patients who are experiencing delirium from an anticholinergic (e.g. \textit{DITROPA\textregistered}, \\textit{DETROL}, \textit{TOVIAZ}), best practice is to discontinue the anticholinergic and use nonpharmacological therapy (moderate fluid intake, scheduled voiding, absorbent products, etc.). [A helpful guide: \url{www.cnca.ca/pdf/Promoting_Continence_Using_Prompted_Voiding.pdf}]

Cholinesterase inhibitors can cause or worsen urinary incontinence.

- Even if not taking a ChEI, the prevalence of urinary incontinence in Alzheimer’s disease patients is >50%.\(^{37}\)
- In patients who are experiencing intolerable incontinence with a ChEI, the first consideration should be to decrease the dose of ChEI and/or to use nonpharmacological therapy. Stopping the ChEI may be necessary.

Given the modest benefits of ChEIs, it is necessary to \textit{prioritize} between anticholinergic & cholinergic therapy.

- This is a situation that may be described as “picking your organ”. Using anticholinergics for the bladder diminishes the therapeutic effect of the ChEI on cognition, and vice versa.\(^{15, 38}\)
- \textbf{Theoretically}, choosing a newer anticholinergic for urinary incontinence could lead to fewer CNS side effects.\(^{38}\)
- M3 receptors are less concentrated in the brain, which has lead to the development of M3-selective agents (e.g. solifenacin \textit{VESICAR\textregistered}, darifenacin \textit{ENABLEX\textregistered}, \textit{TROSEC\textregistered}). Hydrophilic compounds have a limited ability to cross the blood brain barrier, which has lead to the development of agents such as trospium\(^{38}\). In one study, darifenacin did not affect cognitive function in healthy seniors after two weeks.\(^{39}\) In another, trospium was undetectable in the CNS of healthy adults.\(^{36}\) \textbf{These drugs have not been studied in patients with dementia.}

Refer to \url{RxFiles Urinary Incontinence Chart}.

- Note that Saskatchewan Health will discontinue drug coverage for ChEIs when they are combined with highly anticholinergic drugs, as per list on Pg 12.
- Memantine has a unique mechanism of action (see below). It may be considered in patients who do not tolerate cholinesterase inhibitors.

When should cholinesterase inhibitors be avoided or discontinued?

\textbf{Continual assessment of patients on cholinesterase inhibitors is paramount!}

- Common side effects of ChEIs are nausea\(^{11}\), vomiting\(^{21}\), dizziness\(^{15}\), diarrhea\(^{14}\), and headache\(^{14, 17}\). Behaviour disturbances may also occur. It is essential to regularly \textit{ascertain whether side effects outweigh the benefits} of therapy. (Tolerance to side effects can occur over time, especially if the dose of cholinesterase inhibitor is slowly titrated.\(^{17}\))

- **Avoid** cholinesterase inhibitors in:
  - patients with cardiac conduction abnormalities (e.g. sick-sinus syndrome, bradycardia). Syncope, decreased heart rate, and falls have been associated with cholinesterase inhibitors.
  - patients with active peptic ulcer disease. Cholinesterase inhibitors may increase gastric acid secretion and ulcer risk.

- Be cautious in patients likely to experience a drug interaction (see Table 3). Start low and go slow when initiating therapy.

- Evidence suggests that patients whose \textbf{cognitive scores decline rapidly} (i.e. deterioration in ADAS-cog of 4 points or MMSE of 2 points over six months), ChEIs are no better than placebo.\(^{29}\)

- There is considerable debate regarding the best approach for patients who decline from mild or moderate dementia into severe dementia. Cholinesterase inhibitors have been shown to continue to be statistically effective over placebo in preventing cognitive decline in patients with severe dementia.\(^{21}\) However, this may not translate into an improvement in quality of life. \textit{Take into account the patient and patient’s family’s perspectives.}

- If discontinuing a ChEI, a \textit{tapering} process reduces the risk of rebound constipation and other side effects.\(^{47}\) Try decreasing the dose by 25-50% every 1-2 weeks.

- Be aware that many patients will stop ChEIs without talking to their physician. It is common for at least one-third of patients to discontinue therapy within the first six months due to side effects, forgetfulness, cost, or a perceived lack of benefit.\(^{17, 18}\)

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
**ChEi Drug Holidays?** & \\
\hline
There is controversy regarding stopping cholinesterase inhibitor therapy, and then restarting if cognitive decline accelerates. There is limited evidence that patients in this situation may not regain function when the drug is restarted; neuroprotective effects may have been lost.\(^{20}\) On the other hand, discontinuation in patients with severe dementia may be well tolerated.\(^{36}\) & \\
\hline
\end{tabular}
\end{table}
What about memantine?

- Memantine is a NMDA antagonist and therefore presents an alternate mechanism of action for treatment of dementia. Memantine has been studied against placebo, against ChEIs, and in combination with ChEIs. It has an approved indication for moderate to severe dementia caused by Alzheimer’s disease. Memantine does not appear to be effective in mild AD.

- Memantine may have a lesser magnitude of effect than ChEIs. It has been associated with a decrease in aggression & agitation, although this evidence is not rigorous. Theoretically, using memantine in combination with a ChEI is reasonable, but it does not appear to convey additional benefit; it may also be associated with more side effects.

- Side effects include: dizziness, drowsiness, confusion, insomnia, and headache. Caution is required when using memantine in patients with a history of heart disease due to an association with adverse CV events.

<table>
<thead>
<tr>
<th>Table 4. When to consider memantine instead of a ChEI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
</tr>
<tr>
<td>1. Unique side effect profile. May be useful if patient experiences urinary incontinence, diarrhea, or nausea with ChEI.</td>
</tr>
<tr>
<td>2. Approved for moderate and severe dementia.</td>
</tr>
<tr>
<td>3. May be helpful for patients who are aggressive, agitated.</td>
</tr>
<tr>
<td>4. Minimal drug interactions.</td>
</tr>
</tbody>
</table>

What about vitamin E, vitamin B12, omega-3s, ginkgo, atorvastatin..., for the prevention of dementia?

There is insufficient evidence to recommend these products. (see also Geri-RxFiles – Dementia and Cognitive Impairment)

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**Non-Pharmacological Measures for Dementia Treatment** \footnote{34,35}

*“It is not how much we do – it is how much love we put into the doing.”*  
-Mother Teresa

Non-pharmacological interventions may be more efficacious than pharmacological interventions!33

- **Behavioural therapy**: consider Antecedents, Behaviours, & Consequences (ABC). Gather information about manifestations of behaviour and the sequence of events leading to it; changing antecedents or consequences can lead to a change in behaviour.

- Schedule “pleasant events” e.g. audio-books, crosswords, tea with others, personal grooming, exercise.

- **Art therapy, music therapy, aromatherapy, & activity therapy** may offer significant benefit.

- **Reminiscence therapy**: reliving of past pleasurable experiences.

- **Adjust environment** to ability (e.g. safe objects for manipulation; reduced clutter; familiar cues like paint around the toilet, high-contrast steps; increased natural lighting; posted signs).

- **Simulate presence** therapy – audio-recording of family member talking about past positive events; played strategically.

Refer to [RxFiles An Introduction to the Various Types of Dementia, Their Management & Treatment](#)

**Beware of thinking “nothing can be done”. Non-drug therapy often has a substantial impact!!!**

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**----- PEARLS -----**

- Ensure that patients with dementia are not taking drugs with anticholinergic properties. Refer to [Anticholinergic List, Pg 12.](#)

- Prescribe ChEIs with pre-defined criteria for how to evaluate efficacy. Constant re-assessment is a must if one is to avoid excessive costs and excessive side effects for patients and their families.

For some patients, it may be reasonable to trial a ChEI. After trialing, it will often also be reasonable to taper & stop.

- Donepezil may be the best tolerated ChEI. \footnote{17} Dosing donepezil at bedtime & with food may improve GI-related tolerability. If insomnia occurs, dosing may be changed to the morning. \footnote{17,33}

- Intolerable side effects are often best treated by decreasing the dose, switching to a different agent, or tapering & discontinuing therapy.
Dementia & Cognitive Impairment

**The Various Types of Dementia**

Dementia is a term that describes a decline in a variety of functions (e.g. memory, language, motor activities, ability to recognize or identify objects, complex decision-making) which eventually causes a person to have difficulty performing everyday activities. There are different types of dementia which vary in their onset of symptoms, type of symptoms, eventual outcome & response to interventions. Although Alzheimer’s dementia is the best known, other dementias are common, & individuals may have a mix of various dementias.

**Alzheimer’s Disease (AD)**

- AD is associated with typical changes in the brain, often referred to as "plaques", "tangles" & cerebral atrophy (brain shrinkage), which are likely caused by a combination of genetic & environmental factors. While the brain undergoes structural changes, the diagnosis of AD is determined based on a general medical & psychiatric exam (cognitive testing is integral). The diagnosis of AD can only be confirmed upon autopsy.
- There is usually a slow, progressive decline, although individuals occasionally appear to have faster declines at certain points, especially at times of major change, such as widowhood or a move to a new home.
- Short-term memory problems are usually the first sign, but over time the individual develops problems in all other areas of functioning so that he/she will need full-time care.
- Life expectancy:
  - On average 8 to 10 years after symptoms begin
  - If diagnosed in 60s & early 70s, 7 to 10 years
  - If diagnosed in 90s, 3 years

**Frontotemporal Dementia (FTD)**

- FTD has a stronger genetic pattern of inheritance than AD & vascular dementia (VaD), and usually starts earlier in life (often by the 40s or 50s). There are a few different types of FTD. Some affect mostly speech & language in the early stages, but the FTD behavioural variant (FTD-bv) typically affects behaviour first & can be difficult to differentiate from other psychiatric problems.
- Damage is initially limited to the frontal & temporal lobes, which results in a very different pattern of symptoms than AD. Affected individuals usually have an early alteration in their speech, language, personality or social behaviour, before any memory changes occur. The individual often displays poor judgment & inappropriate, disinhibited behaviour more similar to very young children (such as putting everything in the mouth). Certain movements may be performed repetitively without any apparent reason.
- Speech may be very unusual, with repetition of words & sounds, & choppy rhythm. Eventually the individual becomes mute & often also develops difficulties with swallowing. This is particularly common if the individual develops ALS (also known as Lou Gehrig's Disease) with the FTD, which occurs in a sizable percentage of affected individuals.
- Over time, problems arise in other functions as well, resulting in a global dementia, requiring a highly structured environment.
- Life expectancy: 6 to 8 years after symptoms begin

**Lewy Body Dementia (LBD)**

- LBD is associated with similar microscopic changes as Parkinson's Disease (PD), but clinically presents with earlier short-term memory loss, and later Parkinsonism (such as tremor, balance & walking problems & stiffness). Impairment in attention, executive functioning (complex thinking & judgment) & visuo-spatial skills occurs earlier than in AD. There is also more daily fluctuation in all of these abilities than in AD.
- Well-formed & detailed visual hallucinations are common, especially in the evening, but unfortunately, the usual treatment of these symptoms is with antipsychotics, which cause worsening of Parkinson's type symptoms; however, hallucinations do not always warrant treatment unless they are causing distress to the individual or caregivers.
- Falls are very common.
- Unlike AD, in the early stages of LBD the abilities of the affected individual often fluctuate drastically from day to day, or even during the course of a single day. This can often be puzzling for those around them.
- Life expectancy: 6 to 12 years after symptoms begin

**Parkinson’s Disease (PD) Dementia**

- Individuals with PD are prone to developing dementia, which might be typical AD, or more similar to LBD as described above.
- Similar to LBD, there is more impairment in attention, executive function & visuo-spatial skills than in AD.
- Common difficulties include memory loss, apathy, changes in personality & mood, visual hallucinations, & paranoid delusions, especially late in the course of the disease when high doses of medications are required for the treatment of PD.

**Vascular Dementia (VaD)**

- VaD is caused by problems with small or large blood vessels, which may cause poor blood flow to parts of the brain, or bleeding into the brain. Risk factors for developing this include high blood pressure, high cholesterol, smoking, diabetes & heart disease.
- Sometimes individuals with VaD have a history of obvious, clinical strokes, but more often functional changes are associated with more subtle damage seen on brain scans.
- Deficits are often patchy, depending on the areas of the brain affected. The onset may be abrupt, with a stepwise decline, but may also be gradual. Sometimes individuals with VaD are stable for a long time, unlike those with Alzheimer’s disease, whose decline is more progressive.
- Problems with complex thinking, attention, moodiness, depression, apathy, disinhibition, agitation, aggression & occasionally psychosis (hallucinations & delusions) are more common early in the disease than is the case in AD.
- Individuals with VaD tend to maintain their personality & more normal levels of emotional responsiveness until the later stages of the disease. This sometimes means that individuals with VaD are more aware of their condition and more prone to depression than individuals with AD.
- Life expectancy: 5 years after symptoms begin (in many cases, death will be caused by a stroke or heart attack)
## Dementia & Cognitive Impairment

### Approach to the Treatment of Dementia
- Optimize the management of co-morbid conditions.
- Attempt to decrease medications that may worsen cognition/function.

### Medications That Can Cause &/or Contribute to Cognitive Impairment

<table>
<thead>
<tr>
<th>A</th>
<th>P</th>
<th>N</th>
</tr>
</thead>
</table>
| **Anticholinergic Medications**  
See Section 24 for a more complete list | **Psychoactive Medications (usually dose-related)** | **Non-Psychoactive Medications** |
| Antibiotics (e.g. fluoroquinolones [ciprofloxacin], clarithromycin) | P | N |
| Anticonvulsants  
- could be due to drug interactions  
- altered pharmacokinetics can result in CNS toxicity within “normal” therapeutic range | A | P |
| Antidepressants (e.g. paroxetine, SSRIs & TCAs)  
- all serotonin agents, including TCAs & SSRIs, due to SSRI-induced hyponatremia? | A | P |
| Antiemetics / Antivertigo (e.g. dimenhydrinate) | A | P |
| Antihistamines / Antipruritics (e.g. hydroxyzine) | A | P |
| Antimuscarinics (e.g. oxybutynin) | A | P |
| Antiparkinson Meds (e.g. levodopa/carbidopa, pramipexole, ropinirole, amantadine) | A | P |
| Antipsychotics (e.g. olanzapine, quetiapine, risperidone) | A, P | A|
| Class 1A Antiarhythmics (e.g. disopyramide, quinidine, procainamide) | A | P |
| Corticosteroids (e.g. prednisone) | A | P |
| Digoxin  
- digoxin toxicity can occur with “normal” serum digoxin concentrations | A | P |
| H2RAs (e.g. cimetidine, ranitidine) | A | P |
| Hypnotics / Sedatives (e.g. benzodiazepines especially long-acting, high dose) | A | P |
| NSAIDs (e.g. diclofenac, indomethacin) | A | P |
| Opioid Analgesics (e.g. codeine, oxycodone, morphine, hydromorphone, fentanyl) | A | P |

### Assessment of Cognitive Function

The assessment of cognitive function in individuals with dementia is most commonly performed using the Mini Mental State Examination (MMSE). The MMSE consists of 11 questions that test 5 areas of cognitive function: orientation, registration, attention & calculation, recall, & language. The maximum score is 30. It only takes 5 to 10 minutes to administer the MMSE and therefore it is practical to use repeatedly & routinely. The MMSE has been validated to screen for cognitive impairment with older, community dwelling, hospitalized and institutionalized adults.

#### Severity of Impairment
<table>
<thead>
<tr>
<th>Presentation of Symptoms</th>
<th>MMSE Score</th>
</tr>
</thead>
</table>
| **Mild Cognitive Impairment**  
(preclinical) |  
- Report by individual or caregiver of memory loss  
- Objective signs of memory impairment  
- No functional impairment | 26-30 |
| **Early, Mild Impairment**  
(year 1 to 3 from onset of symptoms) |  
- Disoriented to date  
- Naming difficulties (anomia)  
- Recent recall problems  
- Mild difficulty copying figures  
- Decreased insight  
- Social withdrawal  
- Irritability, mood change  
- Problems managing finances | 21-25 |
| **Middle, Moderate Impairment**  
(year 2 to 8) |  
- Disoriented to date place  
- Comprehension difficulties (aphasia)  
- Impaired new learning  
- Getting lost in familiar areas  
- Impaired calculating skills  
- Delusions, agitation, aggression  
- Not cooking, shopping, banking  
- Restless, anxious, depressed  
- Problems with dressing, grooming | 11-20 |
| **Late, Severe Impairment**  
(year 6 to 12) |  
- Nearly unintelligible verbal output  
- Remote memory gone  
- No longer grooming or dressing  
- Incontinent  
- Motor or verbal agitation | 0-10 |

### Note
- Cognitive performance is influenced by number of years of formal education.

---

**Refer to the Alzheimer Society – Caregiver Support & Resources**

The Alzheimer Society provides services & support at the time of diagnosis & throughout the duration of the disease. Individuals & their families are linked to learning, services & support as early as possible in the disease process (e.g. First Link).

**First Link** helps to assist physicians, health care providers, & community service providers to connect individuals living with Alzheimer’s disease & other dementias, & their families, with the Alzheimer Society.

Visit [www.alzheimer.ca](http://www.alzheimer.ca) or call 1-800-263-3367 (SK) for a referral form & more information.
The page provides information on cognitive impairment and the use of cholinesterase inhibitors in managing dementia. It discusses the treatment considerations for dementia, including the potential benefits of treatment and considerations for medications. The page includes details on cholinesterase inhibitors continued, with specific recommendations for rivastigmine and memantine. It also mentions memantine as a NMDA receptor antagonist and provides information on combination therapy involving cholinesterase inhibitors and memantine. The content is presented in a structured format with tables and bullet points for easy reference.
## Dementia & Cognitive Impairment

<table>
<thead>
<tr>
<th>Potential Adverse Events Associated with Treatment</th>
<th><a href="http://www.rxfiles.ca">www.rxfiles.ca</a></th>
</tr>
</thead>
</table>

### Cholinesterase Inhibitors (donepezil, Aricept, galantamine, Reminyl, rivastigmine, Eldepryl)
- Many individuals experience adverse effects (NNH=12). Most common: nausea, loss of appetite, vomiting & diarrhea. The incidence of adverse events ↑ with dose ↑.
- The adverse effects become more tolerable over a few weeks. Slow titration, administration with food, & an antiemetic may improve tolerability.
- Possible adverse effects include: nausea & vomiting, diarrhea (~10%), anorexia, weight loss (~3%), insomnia, agitation (initially), cholinergic effects (e.g. incontinence, stomach, bradycardia, syncope, falls, nightmares), ↑ risk of GI bleed (due to ↑ central & peripheral cholinergic simulation - Particularly in individuals with ulcer disease or those taking anti-inflammatories), QT prolongation (<1% incidence) – donepezil & galantamine. Behaviour disturbance may also occur.

### Memantine
- Use with caution in patients with cardiovascular disease or a history of seizures
- Possible adverse effects include: dizziness, constipation, confusion, insomnia, headache, hypertension, inner & motor restlessness, akathisia, nausea; QT prolongation (<1% incidence)

### Balancing the Risks vs the Benefits
- Cholinesterase inhibitors produce, on average, small improvements in measures of cognition & ADL
  - NNT “improved” on a global assessment scale (CGIC or CIBIC+) = 12
  - NNT 4-point or greater improvement on ADAS-cog = 10
  - NNH adverse event = 12
  {Note: trials done is more healthy patients, & benefits may be less in real life.}
- May slow progression by months, not years
- Not all individuals benefit, but some may “feel better”
- Many cannot tolerate the side effects – marginal benefits may be outweighed by harms that ↓ quality of life

### When Do the Risks Likely Outweigh the Benefits?
- In the frail elderly, especially with multiple co-morbidities
- Problematic urinary incontinence
- Individuals with significant weight loss
- Individuals with significant behaviour problems (agression, agitation)
- Individuals with financial restrictions (e.g. if you had $20 to spend, where would it best be spent?)
- Individuals with severe dementia

### When to Follow-up After the Initiation of Treatment
- **At 1 month**: follow-up to assess for adverse events & a possible increase in dose
  - Consider continuing if improvement is noted either on bedside testing (MMSE) or by the family/caregivers (FAQ).
  - Consider discontinuation if there has been no improvement.
- **Every 6 months afterward**

**Remember**: cholinesterase inhibitors are a symptomatic treatment & not disease-modifying. Administer for 8 weeks at the recommended or maximum tolerated dose & then review the individual’s response with the family and/or caregivers.

### How Long Should Cholinesterase Inhibitors be Used?
- Cholinesterase inhibitors can be continued indefinitely, but evidence of benefit in advanced stages is limited (trials were 6 months in duration).
- Because of known side effects & drug costs of continuing therapy, discontinuation of cholinesterase inhibitors should be considered & balanced against possible worsening of cognitive function & greater functional impairment. It is suggested that cholinesterase inhibitors be discontinued when the following are relevant:
  - The individual, caregiver, or substitute decision-maker decides to stop cholinesterase inhibitors after being informed of the risks & benefits of continuation & discontinuation.
  - The individual is non-adherent & continued prescribing would be useless.
  - The comorbidities of the individual make continued use of the agent unacceptably risky or futile (e.g. terminal illness).
  - The individual’s rate of cognitive, functional, or behavioural decline is greater on treatment compared with that before being treated.
  - The individual demonstrates a poor response to the medication (both MMSE & FAQ decline over 6 month period).
  - The individual’s dementia progresses to a stage where there would be no meaningful benefit from continued therapy (e.g. Global Deterioration Scale stage 7). At this advanced stage of the disease, individuals are no longer able to manage basic ADL (e.g. toileting, dressing) & are forgetting their own personal history.
  - The cost of the medication becomes problematic (e.g. EDS coverage lapses once MMSE <10 in Saskatchewan).
- The individual experiences intolerable side effects that are definitely or probably related to the cholinesterase inhibitor. This may include:
  - Aggression, behaviour disturbance, and/or poor sleep
  - Nausea with weight loss
  - Bradycardia
  - GI adverse events (GI bleed; bothersome nausea/diarrhea)
**Dementia & Cognitive Impairment**

**Stopping a Cholinesterase Inhibitor**

When it has been decided that treatment with a cholinesterase inhibitor should be stopped, it is suggested that the dose be tapered before stopping the agent. Caregivers should be warned that discontinuation of pharmacotherapy may cause cognitive & behavioural decline. Taper over 2 to 4 weeks. For example, consider reducing the donepezil dose from 10 mg to 5 mg once daily for four weeks before stopping it. The medication may be restarted if there is a temporal relationship between the discontinuation of the medication & sudden deterioration by the individual.

If discontinued because of perceived lack of effectiveness, it is recommended that the patient be monitored over the next 1 to 3 months for evidence of an observable decline. If this occurs, it is suggested that reinstating therapy be considered. Symptoms may not be fully reversible if there is a delay in restarting pharmacotherapy.

**Can Dementia be Prevented?**

There is no consistent evidence of benefit for any pharmacologic agent in preventing cognitive decline in healthy older adults.

**Anti-inflammatories**

A study conducted over 3 years investigated the use of naproxen & celecoxib among 2500 patients & found a marginal decline in memory with use of the medications; global summary scores were 0.05 standard deviations lower (p = 0.02) in the treatment arm. However potential harms (e.g. GI bleeds) are also known to be significant.

**Cholinesterase Inhibitors**

Cholinesterase inhibitors do not prevent the progression of mild cognitive impairment (MCI) to dementia.

**Dehydroepiandrosterone (DHEA)**

Three RCTs investigated the use of DHEA in a total of 317 patients. Follow-up was from 6 weeks to 1 year. None of the 3 studies showed a statistically significant improvement in cognitive function with the use of DHEA supplements.

**Estrogens**

Studies investigating estrogen therapies have shown evidence of a ↓ in memory & cognitive function, & an ↑ in incident dementia (hazard ratio 1.8, 95% confidence interval [CI] 1.2 to 2.6). The WHIMS was a RCT of estrogen + progestin (n = 2229) versus placebo (n = 2303) for prevention of dementia in women aged ≥65 years. Use of estrogen for a mean of 4 years was associated with a relative risk of 2.05 (CI, 1.21–3.48) for dementia during the study period. There is however some controversy about these findings – some might debate that the ‘type’ or ‘formulation’ of estrogen used plays a role. (i.e. Would bioidentical hormones produce better results versus synthetic or equine derivatives? Would topical formulations, which some consider “safer” than oral formulations, produce better results?)

**Can Dementia be Prevented? - continued**

**Ginkgo**

Two RCTs: 1) Solomon 2002 - 230 cognitively healthy older adults after 6 weeks did not show a significant difference in any cognitive outcome measured; 2) Dodge 2008 - 118 patients over 42 months also found no significant change in cognitive decline between the ginkgo & placebo groups. Ginkgo biloba did not prevent dementia in one prospective trial.

**Vitamins & Fatty Acids**

RCTs have assessed the use of various vitamins and fatty acids for the prevention of cognitive decline. Vitamin B6 (n = 76, study duration 12 wk) vitamin E (n = 6377, study duration nearly 10 yr) folic acid (n = 24, study duration 4 wk) & the omega-3 fatty acid EPA–DHA (eicosapentaenoic acid– docosahexaenoic acid; n = 302, study duration 6 mo) have all been studied, & none showed evidence of preventing cognitive decline. There is some evidence that vitamin E may in fact be associated with increased morbidity & mortality.

**Non-Pharmacological Interventions**

- The evidence for physical activity in preventing cognitive decline is weak. One RCT investigating resistance training in healthy older adults showed improvement in cognitive outcomes.
- Formal cognitive training exercises may have a benefit in preventing cognitive decline. There is consistent evidence that cognitive training using formal programs is effective at preventing cognitive decline based on 3 RCTs.

**Modifiable Risk Factors**

A 2011 meta-analysis identified 7 potentially modifiable risk factors for AD & calculated a population attributable risk or PAR (the percent of cases attributable to a given factor) & CI for each in the United States:

- Cognitive inactivity or low educational attainment (PAR = 7.3% [CI, 4.4–10.3])
- Depression (PAR = 14.7% [CI, 9.6–20.3])
- Diabetes mellitus (PAR = 3.3% [CI, 1.5–5.4])
- Midlife hypertension (PAR = 8.0% [CI, 2.2–15.1])
- Midlife obesity (PAR = 7.3% [CI, 4.3–10.8])
- Physical inactivity (PAR = 21% [95% CI, 5.8–36.6])
- Smoking (PAR = 10.8% [CI, 3.0–19.8])

There may be additional modifiable risk factors, such as wearing a helmet to prevent head injury, not included in the above list.
### Antibiotics

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>TCA</th>
<th>SSRI</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
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<tr>
<td>Cefoxitin</td>
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<tr>
<td>Clindamycin</td>
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<tr>
<td>Gentamicin</td>
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<td></td>
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<tr>
<td>Pipercillin</td>
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<td></td>
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<tr>
<td>Vancomycin</td>
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</tbody>
</table>

### Antimuscarinics

- Darifenacin
- Fesoterodine
- Flavoxate
- Mirabegron
- Oxybutynin
- Solifenacin
- Tolterodine l-tartrate

### Antiparkinsonian

- Amantadine
- Benztrapine mesylate
- Bromocriptine
- Carbidopa/levodopa
- Entacapone
- Ethopropazine
- Pramipexole
- Propyliodine
- Selegiline
- Trihexyphenidyl

### Antipsychotics

- Aripiprazole
- Asenapine
- Chlorpromazine
- Clozapine
- Fluoxetine
- Fluphenazine
- Haloperidol
- Loxapine

### Anticholinergic

- Bupropion
- Desvenlafaxine
- Duloxetine
- Maprotiline
- Mirtazapine
- Moclobemide
- Phenelzine
- Tradodone
- Venlafaxine

### Antidepressants

- Amoxapine
- Clomipramine
- Desipramine
- Dexamfetamine
- Imipramine
- Nortriptyline

### Cardiovascular Agents

- Atenolol
- Captopril
- Clonidine
- Diltiazem
- Lisinopril
- Metoprolol
- Nifedipine
- Quinidine
- Trimaterene

### Gastrointestinal Agents

- Belladonna
- Chlorazepoxide/clidinium
- Cimetidine
- Dicyclomine
- Diphenoxylate/atropine
- Famotidine
- Loperamide
- Metoclopramide
- Nizatidine
- Prochlorperazine

### Antihistamines/Antipruritics

- Brompheniramine
- Chlorpheniramine
- Ciproheptadine
- Dimenhydrinate
- Diphenhydramine
- Hydroxyzine
- Pyrilamine
- Trimipramine

### Antihistaminic

- Dimenhydrinate
- Meclizine
- Promethazine
- Scopolamine

### Antihistamines

- Bronpheniramine
- Chlorpheniramine
- Ciproheptadine
- Dimenhydrinate
- Diphenhydramine
- Hydroxyzine
- Pyrilamine
- Trimipramine

### Non-Sedating Antihistamines

- Levocetirizine
- Loratadine

### Antiseizure Drugs

- Carbamazepine
- Divalproex
- Oxcarbazepine
- Valproic acid

### Immunosuppressants

- Azathioprine
- Cyclosporine

### Muscles Relaxants

- Baclofen
- Cyclobenzaprine
- Methocarbamol
- Orphenadrine
- Tizanidine

### Opioids

- Meperidine
- Codeine
- Fentanyl
- Hydrocodeine
- Hydromorphone

### Respiratory Medicines

- Fluticasone/salmeterol
- Theophylline

### Miscellaneous

- Buspirone
- Colchicine
- Dipyridamole
- Ketotifen
- Pseudoephedrine
- Theophylline

### Other

- Bronpheniramine
- Chlorpheniramine
- Ciproheptadine
- Dimenhydrinate
- Diphenhydramine
- Hydroxyzine
- Pyrilamine
- Trimipramine

### Preferred Alternatives

- Buspirone
- Colchicine
- Dipyridamole
- Ketotifen
- Pseudoephedrine
- Theophylline

### Moderate/High anticholinergic activity

- Low anticholinergic activity

### Special Considerations

- Possible preferred alternatives

### Notes

- Denotes agents with anticholinergic activity that may be better tolerated than others. Whenever possible, anticholinergic drugs should be avoided, & the preferred agents used.
- X = non-formulary in Saskatchewan
- Y = prior approval NIH
- Z = not covered by NIH
- AChEI = Acetylcholinesterase Inhibitor (e.g. Donepezil, Galantamine, Rivastigmine, Ertapenem)

### Acknowledgements

- The authors are grateful to the Canadian Pharmacists Association, the Saskatchewan Pharmacists Association, and the Saskatchewan Health Authority for their contributions to this project.
Dementia: Behavioural & Psychological Symptoms

The behavioural & psychological symptoms of dementia (BPSD) can create a significant caregiver challenge.

BPSD of varying degrees of severity are present in more than 90% of individuals with dementia.¹

<table>
<thead>
<tr>
<th>Common Behavioural &amp; Psychological Symptoms of Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggression (both verbal &amp; physical)*</td>
</tr>
<tr>
<td>Agitation</td>
</tr>
<tr>
<td>Anger, Irritability (screaming)</td>
</tr>
<tr>
<td>Apathy</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Emotional lability, Disinhibition</td>
</tr>
<tr>
<td>Hoarding</td>
</tr>
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<td></td>
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</table>

*Physical aggression may include: biting, destroying property, grabbing, hitting, kicking, pushing, scratching, spitting, throwing items.

**Approach to Managing BPSD**

- **Document the target symptom.**
  - Be specific
    - A number of validated standardized assessment tools are available to assist with the tracking, assessment, & documentation of behaviours such as: the Cohen Mansfield Agitation Inventory, Dementia Observation Scale, & Behaviour Pattern Record.⁵
    - Identify what causes the behaviour & what makes it better or makes it go away
      - The ABC approach is useful: A – Antecedents  B – Behaviour  C – Consequences ⁶
        - Document what happened before the behaviour such as morning care routine, meal, or unprovoked (antecedent), details of the specific behaviour such as if it was verbal, physical or sexual (behaviour), & what happened after the behaviour (consequence).
        - Look for patterns after recording the behaviour several times.
    - Identify whom the behaviour is bothering (the individual, caregivers, other residents)

- **Assess for any triggering factors** (not an exhaustive list):

<table>
<thead>
<tr>
<th>PSYCHOLOGICAL Triggers</th>
<th>MEDICAL Triggers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distress</td>
<td>B12/Folic Acid Deficiency</td>
</tr>
<tr>
<td>Fear of Danger</td>
<td>Constipation or Fecal Impaction</td>
</tr>
<tr>
<td>Feeling Abandoned</td>
<td>Hunger or Thirst</td>
</tr>
<tr>
<td>“Bad Company” (not liking who is around)</td>
<td>Hypercalcaemia</td>
</tr>
<tr>
<td>Boredom</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Confusing Surroundings</td>
<td>Infection (e.g. pneumonia, UTI)</td>
</tr>
<tr>
<td>Excessive Demands</td>
<td>Metabolic (e.g. hyponatraemia)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ENVIRONMENTAL Triggers</th>
<th>MEDICATION Triggers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of Autonomy or Control</td>
<td>Acetylcholinesterase Inhibitors (e.g. donepezil, rivastigmine)</td>
</tr>
<tr>
<td>Misinterpretation</td>
<td>Anticholinergic Medications (see page 24A)</td>
</tr>
<tr>
<td>Loneliness</td>
<td>Anticonvulsants (e.g. carbamazepine, phenytoin)</td>
</tr>
<tr>
<td>Low Lighting</td>
<td>Anti-Parkinson Medications (e.g. levodopa/carbidopa)</td>
</tr>
<tr>
<td>Noise / Sounds / Certain Music</td>
<td>Benzodiazepines (e.g. lorazepam)</td>
</tr>
</tbody>
</table>

- **Determine if the symptom requires treatment.**
  - Some behaviours or psychological symptoms may not require treatment if they are not problematic, or treatment risks may outweigh potential benefits.
    - It may be appropriate to allow for wandering within limits. Locked neighbourhoods (unit or wing) in long-term care homes may allow for this behaviour if an individual is not wandering into the rooms of other residents & disturbing them.
    - Hallucinations & delusions may not require treatment if they do not cause distress to an individual. For example, if an individual is hallucinating that a family member is present & he/she is pleasantly conversing with the “imagined” family member, treatment of the hallucination would not be required.

**Non-Pharmacologic Interventions vs Pharmacologic Treatment**

- **Use non-pharmaceutical measures whenever possible.**
  - Non-pharmacologic interventions have often been shown to be more effective than pharmacologic treatment for dementia-related behavioural problems & should be attempted first, whenever possible. They also address behavioural triggers & avoid the problems associated with pharmacologic interventions (e.g. adverse events, drug interactions, & limited efficacy).⁷

If the individual/resident or caregivers are at risk of harm or danger, sole reliance on non-pharmacological measures may not be appropriate, & pharmacologic options may be required. However, with ongoing efforts to train caregivers & staff, less reliance on medications can be realized over time.
### Non-Pharmacologic Treatments

#### Non-Pharmacological Treatment for PSYCHOLOGICAL Triggers
- Show a warm, kind, matter-of-fact manner
- Make eye contact (if culturally appropriate)
- Use the individual’s name
- Provide simple step-by-step instructions
- Ask questions with limited choices such as “Would you like water or milk?” rather than “What would you like to drink?”
- Avoid social isolation (but observe the impact of various social environments on mood)
- Facilitate or arrange for spiritual care when appropriate
- Allow the individual to make decisions whenever possible
- Reassure & redirect the individual
- Avoid frequent corrections, e.g. “Please do this,” instead of “Don’t do this”
- Stay calm and patient when speaking & avoid tense body language
- Don’t argue with an individual
- Don’t talk about the individual as if he/she is not there or speak ill of other residents in their absence (remember, some residents have excellent hearing)

#### Non-Pharmacological Treatment for ENVIRONMENTAL Triggers
- Encourage the individual to use his/her glasses or hearing aids (caution in noise sensitive individuals)
- Assist with appropriate physical exercise such as a walk
- Provide regular daily routine, activities & structure
- Provide a comfortable, familiar living environment (e.g. obtain pictures, ornaments from home, pet therapy with a familiar animal)
- Engage the individual in simple daily activities that he/she is able to do
- Avoid overstimulation (noise, TV, crowds)
- Refer individuals to adult day care programs if needed and as available
- Consider aromatherapy or music therapy (find out what type of music the individual enjoys)
- Other useful activities to consider: gardening, music & dancing, art, interactions with a pet, group activities (e.g. singing, crafts)

#### Non-Pharmacological Treatment for MEDICAL Triggers
- Offer food & drink
- Treat symptoms such as pain, constipation, urine retention, nausea, dyspnea, if present
- Evaluate & treat endocrine & metabolic disorders (blood sugar, thyroid, etc)
- Evaluate & treat infections according to goals of care (pneumonia, UTI, dental caries)
- Evaluate & treat cardiovascular disorders according to goals of care

#### Non-Pharmacological Treatment for MEDICATION Triggers
- Discontinue medications that may be contributing to the BPSD, when possible (taper or ↓ dose)

---

### What are the Pharmacologic Options?

Treatment options for BPSD are dependent upon the symptom(s) that an individual is experiencing. When pharmacological interventions are initiated, ensure that a clear goal of therapy has been identified. Also ensure that a monitoring plan & evaluation plan of progress are clearly defined.

The following sections explore the various treatment approaches for both the behavioural disturbances associated with dementia, & the psychological symptoms of dementia.

#### Anxiety

Use non-pharmacological interventions whenever possible & minimize provocation.

Anxiety may be chronic in nature or may be intermittent & caused by anxiety provoking situations.

- For **CHRONIC** anxiety:
  - Consider **antidepressant therapy** if anxiety is secondary to depression or very chronic in nature (this is addressed in a following section entitled “Depression”).
    - Antidepressants with anxiolytic properties: citalopram **CELEXA**, sertraline **ZOLOFT**, venlafaxine **EFFEXOR XR**, trazodone **Desyrel**, moclobemide **Manerix**.
  - Buspirone: 10 to 30mg per day, divided BID to TID (possibly as high as 60mg/day)
    - Has a delayed onset of ~3 weeks when used for chronic anxiety (may limit its usefulness)
    - Compared to benzodiazepines, buspirone is less sedating, has fewer drug interactions, causes less withdrawal & less impairment of motor function
    - The best response will be achieved in individuals who are benzodiazepine naïve
  - Clonazepam: 0.125 to 2mg per day, divided BID to TID
    - Long-acting benzodiazepine (half-life ~34 hours)
    - Long-acting benzos are not frequently recommended in older adults except for in certain circumstances, including severe generalized anxiety
    - See cautions below (e.g. falls, cognitive impairment, disinhibition)

- For **INTERMITTENT** anxiety:
  - Use agents short-term (<1 month while waiting for antidepressant to work) & only as-needed
  - Intermediate-acting benzodiazepines may be most appropriate if used short-term for anxiety states or before planned anxiety provoking situations (e.g. bathing, dental work)
    - Lorazepam **Ativan**: 0.5 to 1mg prn, up to TID (available as a sublingual tablet)
    - Oxazepam **Serax**: 10mg BID to TID may be a suitable alternative

#### Benzodiazepine CAUTIONS

- Can cause sedation, ataxia (lack of muscle control during voluntary movements), altered sleep architecture, night wandering, motor impairment, cognitive impairment, confusion, paradoxical excitation, disinhibition, falls.
- Withdrawal symptoms can occur when discontinued, therefore tapering required.

For more information on the management of specific symptoms related to dementia, see RxFiles: An Introduction to the Various Types of Dementia, Their Management & Treatment.
Apathy\textsuperscript{15, 16} is defined primarily as a loss of motivation & reduced emotional reactivity. Treatment with external activity & environmental measures likely most effective.

Pharmacotherapy may be an option, but some agents such as antidepressants may worsen apathy. Occasionally, stimulants may be helpful, but present an array of problematic adverse effects. Cholinesterase inhibitors may also help somewhat (anecdotal).

- **Methylphenidate** \textsuperscript{Ritalin} : 5 to 20mg BID to TID (Off-label use: depression; the recommended initial dose is 2.5mg in the morning)
  - Common adverse events reported: ↑ blood pressure, ↓ appetite/weight loss, dizziness, sleep disturbance, irritability, delusions, restlessness, agitation, ↑ heart rate. This medication may also present diversion concerns.

### Depression

Pharmacologic options should not be used to treat mild depression, & should be reserved for moderate to severe depression. These agents may improve depression, depression associated agitation, emotionality & irritability. They may also improve some behaviours such as disinhibition. Antidepressant medications may worsen apathy in some individuals.

Allow >6 weeks for adequate trial at an adequate dose. **Start low, go slow, but go!**

- **Selective Serotonin Reuptake Inhibitors (SSRIs)** - first-line for depression, best tolerability\textsuperscript{17}
  - **Citalopram** \textsuperscript{Celexa} : 10 to 20mg daily **CAUTION**: doses >20mg are not recommended due to the risk of QT prolongation (see Section 7)
    - Citalopram has the best evidence for reducing agitation & aggression\textsuperscript{18, 19}
  - **Escitalopram** \textsuperscript{Cipralex} : 5 to 10mg daily **CAUTION**: doses >10mg are not recommended due to the risk of QT prolongation (see Section 7)
    - Escitalopram also available in an orally disintegrating formulation
  - **Sertraline** \textsuperscript{Zoloft} : 25 to 100mg daily
  - **Fluoxetine** \textsuperscript{Prozac} : 25 to 150mg daily at bedtime (sedating, many drug interactions)

- If possible, avoid **fluoxetine** \textsuperscript{Prozac} due its long-half life & avoid **paroxetine** \textsuperscript{Paxil} due to its anticholinergic properties. Both these agents have many drug interactions. May consider these options if they were previously effective. (Fluoxetine also available in liquid form commercially.)

Possible adverse events to monitor for: nausea, vomiting, restlessness, falls, insomnia, weight loss, agitation (especially upon initiation), hyponatremia, bleeding (e.g. stroke, upper GI, bruising).

### Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

- **Venlafaxine** \textsuperscript{Effexor XR} : 37.5 to 150mg daily
  - The XR capsule can be opened & sprinkled on applesauce while maintaining its 24 hour action – do not chew spheres/granules.
  - Adverse events are similar to those of SSRI, but with more common GI events, & may ↑ blood pressure. High risk of withdrawal syndrome; gradual tapering important.

### Tricyclic Antidepressants (TCAs)

- **Nortriptyline** \textsuperscript{Aventyl} : 10 to 50mg at bedtime *likely the best tolerated TCA in older adults – least hypotensive TCA & less anticholinergic than 3° TCAs (e.g. amitriptyline)
  - **Desipramine** \textsuperscript{Norpramin} : 25 to 100mg daily at bedtime
  - If possible, avoid 3° TCAs due to their greater anticholinergic activity (i.e. amitriptyline, clomipramine, doxepin >6mg/day, imipramine, & trimipramine)

Possible adverse events include: hypotension, blurred vision, urinary hesitancy, QT prolongation (less likely with nortriptyline – see Section 7)

- If dry mouth is a problem, consider a “saliva substitute” product to minimize this adverse effect

### Others

- **Buproprion** \textsuperscript{Wellbutrin SR/XL} : 100 to 150mg BID (SR) or 150 to 300mg daily (XL)
  - May help activate an individual with withdrawal or psychomotor retardation.
  - Lowers seizure threshold [dose-dependent; low risk when dose ≤ 400mg/day [0.4%]].
- **Mirtazapine** \textsuperscript{Remeron} : ≤7.5 to 30mg at bedtime (can start as low as 3.75mg to minimize adverse effects)
  - Consider for individuals with co-morbid anorexia, anxiety, or sleep difficulties.
  - Orally disintegrating formulation available (if difficulty swallowing).
- **Moclobemide** \textsuperscript{Manerix} : 100mg daily to 300mg BID
  - May help with anxiety.
  - Can cause restlessness/↑ stimulation.

Notes:
Dementia: Behavioural & Psychological Symptoms

### Psychosis, Agitation & Aggression

The pharmacologic treatment of behavioural disturbances in dementia is of limited efficacy & should be used after non-pharmacologic interventions have been implemented, if appropriate. Pharmacological interventions may be appropriate for **PSYCHOSIS, AGITATION OR AGGRESSION** if the behaviour:

- Is causing harm or significant distress to the individual themselves, caregivers or others living in the same home AND is persistent or recurrent
- Has not adequately responded to non-pharmacological interventions (& an effort has been made to exhaust all possible non-pharmacological measures)
- Is not due to reversible or treatable causes (e.g. a physical cause or medication-induced)
- The behaviour is moderate to severe (as opposed to mild)

Remember to ask: “Is my patient’s/resident’s behaviour change possibly due to a drug or medical condition?” before asking for a drug to manage it.

### Antipsychotics

- The effectiveness of antipsychotics for BPSD is modest, & clinical value is limited due to serious adverse events.
- In BPSD trials, placebo response rates are often ~40%, reflecting the high rates of spontaneous resolution & the value of psychosocial input in such trials.
- The more severe the behaviour or symptom, the better the response to antipsychotics
- Antipsychotics should not be routinely used long-term for BPSD. Thus, they should be reviewed for possible taper & discontinuation every 3 months.
- Both older (typical) & newer (atypical) antipsychotics have been studied in BPSD; atypical antipsychotics are often preferred to help manage BPSD (but not acute delirium).
- The most commonly used atypical antipsychotics include: risperidone (**Risperdal**), olanzapine (**Zyprexa**, **Seroquel**), & quetiapine (**Seroquil**). Aripiprazole (**Abilify**) & clozapine (**Clozaril**) may also be used.
  - Haloperidol (**Haldol**) is appropriate for acute delirium (discussed in more detail elsewhere.)

Consider the balance of the potential benefits of treatment with an antipsychotic (e.g. may improve safety of the individual &/or others [family, staff]; may ↑ quality of life) versus potential harms relative to alternative treatment. Discuss with the individual/resident &/or family.

The use of antipsychotics for BPSD has received a lot of attention due to the concerns related to the overuse of this class of medication for the treatment of BPSD. There are some controversies regarding off-label marketing of antipsychotics in dementia; however, antipsychotics have a valid role when behaviour challenges outweigh safety concerns.

One is sometimes stuck with the harm of using vs the harm of not using.

### Potential Harms Associated with Atypical Antipsychotics:

- ↑ weight, hyperlipidemia, hyperglycemia
- Sedation, lethargy
- Falls; postural hypotension
- Confusion, agitation, delirium, akathisia (restlessness) → due to anticholinergic & antiparkinsonian effects
- Extrapyramidal effects (EPS): drooling, rigidity, stiffness, akinesia (a slowness or loss of normal motor function resulting in impaired muscle movement)
- Tardive dyskinesia (involuntary, repetitive body movements)
- Infections (respiratory & urinary tract)

### Stroke

- The risk (odds ratio) is about 1.3 to 3.1. That is to say that an individual who is taking an atypical antipsychotic for BPSD is 1.3 to 3.1 times more likely to have a stroke as a result of the use of this class of medication.
- No one antipsychotic is considered to be safer than another in terms of stroke, however some studies have found that risperidone may have a greater risk of stroke. Higher doses, older age, a diagnosis of dementia (especially vascular dementia), & comorbid atrial fibrillation have been noted as risk factors for stroke.
- The risk remains elevated for ~20 months after the initiation of treatment.

### Possible ↑ risk of mortality

This is a somewhat controversial issue. There are limitations & potential confounders with the available data that leave us uncertain about the magnitude of the harm. Keeping this in mind, it is sometimes suitable to prioritize quality of life over prolongation of life when treating BPSD.

- The risk of death is about 1.2 to 1.6 times higher in individuals who take antipsychotics versus those who do not (placebo group).
- The most common conditions associated with cause of death are: pneumonia, cardiac failure & cardiac arrest (related to QT prolongation – see page 7B).
  - The risk of cardiac death ↑ with ↑ dose (dose-related)
- No one antipsychotic is considered to be safer than another in terms of death, although two cohort studies have reported that quetiapine has the lowest mortality risk, compared to risperidone & olanzapine.
  - For risperidone: reference (risk = 1)
  - For olanzapine: relative risk = 1.02 (95% CI 0.92 to 1.12)\(^{35}\); no difference (i.e. olanzapine & risperidone demonstrate no difference in risk of mortality)
  - For quetiapine: relative risk = 0.76 (95% CI 0.7 to 0.82)\(^{17}\); (0.81, 0.75 to 0.88)\(^{38}\) (i.e. risperidone, carries a 24% greater mortality risk compared to quetiapine, likely associated with the lower dosages of quetiapine used)
- Older age, male gender, severe dementia, & functional impairment are associated with a higher risk. Dose of the medication may also play a role for all antipsychotics, except quetiapine.
  - For risperidone, the hazard ratio is 1.35 for high dose (>1mg), & 1.19 for medium dose (0.5 to 1mg)\(^{40}\)
  - For olanzapine, the hazard ratio is 1.36 for high dose (>5mg), & 1.19 for medium dose (2.5 to 5mg)\(^{41}\)
- The risk remains elevated in the first 30 to 120 days, & possibly up to 2 years after the initiation of treatment.
- Stopping treatment has been associated with a reduction in mortality (DART-AD).
Dementia: Behavioural & Psychological Symptoms

- Start low, & go slow!

  Some tips to help minimize potential adverse events, & maximize the efficacy of the medication when initiating an antipsychotic for aggression, agitation or psychosis due to dementia:
  - The starting dose should be as low as possible.
    - The starting dose can be divided or timed according to the behaviour. For example, lunchtime dose for individuals exhibiting increased agitation toward the end of the day.
    - The dose can be titrated up, in small increments, every 1 to 2 weeks, depending on response.
  - Aim for an improvement in target symptoms, not resolution.
    - If a positive response occurs, it is usually evident within 2 weeks, but it may take longer.

- Atypical Antipsychotics

  - **Risperidone**: 0.25 to 2mg daily or divided BID
    - The only atypical antipsychotic with an official indication for use in BPSD.
    - At higher doses, it may behave more like a typical antipsychotic in terms of a higher incidence of extrapyramidal effects.
  - **Olanzapine**: 1.25 to 7.5mg daily or divided BID
    - May be modestly effective for treating agitation, but generally not recommended in individuals with dementia. Olanzapine’s anticholinergic properties can be particularly problematic in older adults, also associated with rapid & significant weight gain (in some older adults), sedation, & hyperglycemia.
  - **Quetiapine**: 12.5 to 100mg daily (may use as high as 150mg daily or in some situations 200mg daily). Higher doses can be split into two or more divided doses.
    - Of the atypical antipsychotics, quetiapine is the best option in individuals with Parkinson’s or Lewy Body Dementia due to the risk of EPS (e.g. less stiffness) compared to other atypicals.

- Monitor closely for adverse events. Reassess in 3 to 7 days after the initiation of treatment, & regularly afterward for adverse events.

  Older adults are especially vulnerable to the adverse effects of antipsychotics, & these may outweigh any benefits. Adverse effects are generally dose-related & can be minimised by keeping the dose as low as possible.

With atypical antipsychotics, monitor for:

- **CNS depression**: sedation, increased confusion or cognitive impairment.
- **Anticholinergic effects**: dry mouth, constipation, urinary retention, blurred vision, delirium – especially with olanzapine & quetiapine.
- **Dizziness & postural hypotension**: increases risk of falls – especially with risperidone & quetiapine.
- **Extrapyramidal effects (EPS/movement disorders)**: ↑ muscle stiffness or rigidity, dyskinesias, dystonias – occur more frequently with higher doses of risperidone.
- **Metabolic changes**: not observed frequently in older adults, monitor weight & possibly A1C if co-existing diabetes or impaired glucose tolerance.
- **Infection**: antipsychotic use is associated with an increased incidence of infections, in particular urinary infections & pneumonia.

Combination & prn use of Antipsychotics

**CAUTION**: potential for overuse of prn or combination use.

Regular scheduled dosing is generally preferred over prn "as needed" antipsychotics.

There is no evidence for using a combination of two different antipsychotics.

There is no evidence for combination therapies with antipsychotics for BPSD (i.e. no added benefit), but there is an ↑ risk of adverse events. To minimize the risk of combination therapy, optimize the dose of the antipsychotic, allow for an adequate trial period (~2 weeks). If there is no response, discontinue the agent & initiate a new agent.

- Regularly review for adverse events AND the need for continuing treatment.

  - Review within 3 to 7 days after the initiation of an antipsychotic or a dose ↑ for both tolerability & adverse events AND review treatment every 3 months to query if the medication is still beneficial / needed. Consider stopping (by taper) every 3 months.

The What, Why & How of Antipsychotic Tapering

**WHAT**: Review antipsychotic use every 3 months, & consider trialing a taper.

- Review the target behaviour, changes in function & significance of adverse effects at least every 3 months, & document in the chart/record. Try tapering the dose or stopping the antipsychotic every 3 months using a slow, gradual taper.

- **CATIE-AD** demonstrated the limited long-term role atypical antipsychotics have in the treatment of BPSD (quetiapine vs risperidone vs olanzapine vs placebo).
  - 80% of participants stopped therapy by 39 weeks due to poor tolerability (based on time to discontinuation due to adverse effects, intolerability or death)
  - Consider routine reassessment in 3-6months for both efficacy & tolerability.
### Dementia: Behavioural & Psychological Symptoms

#### The What, Why & How of Antipsychotic Tapering

**WHY:** BPSD may be short-term & diminish with time, especially when mild-moderate; long-term use of atypical antipsychotics may result in ↑ mortality.

- Dementia & the BPSD will present uniquely in each individual. Some behaviours will decrease in severity & may completely resolve as the dementia progresses.

- **DART-AD** (n=165, age ≈85, Alzheimer’s with MMSE = 11; 2 arms: continuation of an antipsychotic after 3 months of use vs switch to placebo).
  - **Results:** No significant difference in survival at 12 months.
  - **Stopping long-term antipsychotics reduced mortality by ~25% at 2 years** (71% vs 46% survival).
    - Survival at 2 years: 71% placebo group still alive vs 46% antipsychotic group; NNT for discontinuation = 4/2 years (i.e. One person will avoid death for every 4 who were on an antipsychotic for at least 3 months & stopped, at 2 years).
    - Survival over 2 to 4.5 years: 54% placebo group survived vs 38% antipsychotic group; NNT = 8
  - BPDS outcomes: no statistical difference except verbal fluency better in patients who stopped at 6 months.

**HOW:** Reduce dose by 25-50% every 1 to 2 weeks (may be ↓ over longer intervals [e.g. every 4 weeks]).

- Withdrawal of antipsychotics should be done gradually 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.

#### What about haloperidol? 50

- Does not differ significantly in effectiveness from atypical antipsychotics
- Should generally be avoided in older adults given the high risk of extrapyramidal adverse effects & ↑ mortality as the dose is ↑, compared to atypical antipsychotics
- Low-dose haloperidol (0.5mg BID to TID) has a role in the short-term management of the acute symptoms of delirium (except in individuals with Parkinsonism of any cause)

Typical antipsychotics appear to have a ↑ risk of tardive dyskinesia & neuroleptic malignant syndrome. Among typical agents, haloperidol has a ↓ risk of anticholinergic effects, ↓ sedation & minimal weight gain, but a ↑ risk of parkinsonism & akathisia (use low doses 0.25 to 2mg daily) 51

#### What about anticonvulsants (mood stabilizers) for agitation or aggression? 52

There are many limitations to using valproate ([similar to TEGRETOL](https://www.rxfiles.ca)) or lamotrigine ([similar to LAMICTAL](https://www.rxfiles.ca)) for the treatment of BPDS:

- **Valproate:** Current evidence does not support its use & problematic adverse effects 53;
  - Requires lab monitoring
- **Carbamazepine:** Limited evidence, many drug interactions, problematic adverse effects;
  - Requires lab monitoring
- **Lamotrigine:** Evidence limited to case reports & case series; Risk of Stevens-Johnson Syndrome

#### Other Medications & Their Role in BPSD

- **Cholinesterase Inhibitors** ([donepezil](https://www.rxfiles.ca) / galantamine / rivastigmine / exelon)
  - Modest cognitive, functional & behavioural benefit (e.g. NNT=10 for a 4-point or greater improvement on ADAS-cog). Not all individuals will benefit.
  - May help apathy (also hallucination & maybe delusions [post-hoc analysis]);
  - Unlikely to help agitation & aggression (not better than placebo for agitation). 54
  - May help in Lewy Body Dementia to decrease visual symptoms.

- **Memantine**
  - May help agitation, irritability, disinhibition & psychosis, however the evidence is not rigorous 55 56

See Section 21 for more information on cholinesterase inhibitors & memantine

#### Sexually Inappropriate Behaviour

- Assess for medical reasons (e.g. UTI) & any drug causes (e.g. lorazepam, dopamine agonists). Remove disinhibiting drugs including benzos & alcohol.

- **Treatment:** Behavioural intervention 15: redirection, distraction, avoiding stimulants
  - Limited data on drug treatment (SSRIs, antipsychotics, cholinesterase inhibitors)
  - See [RxFiles Hypersexuality Chart](https://www.rxfiles.ca)


Anticholinergic Cognitive Burden Scale http://www.indydiscoverynetwork.org/AnticholinergicCognitiveBurdenScale.html


Han L, Agostini JV, Allore HG. Cumulative anticholinergic exposure is associated with poor memory and executive function in older men. J Am Geriatr Soc. 2008 Dec;56(12):2203-10. Cumulative anticholinergic exposure across multiple medications over 1 year may negatively affect verbal memory and executive function in older men. Prescription of drugs with anticholinergic effects in older persons deserves continued attention to avoid deleterious adverse effects.


Lackner TE, Wyman JF, McCarthy TC, Monigold M, Davey C. Randomized, placebo-controlled trial of the cognitive effect, safety, and tolerability of oral extended-release oxybutynin 5mg/day in cognitively impaired nursing home residents with urge urinary incontinence. J Am Geriatr Soc. 2008 May;56(5):862-70. n=50. 4 weeks. Short-term treatment using oral extended-release oxybutynin 5 mg once daily was safe and well tolerated, with no delirium, in older female nursing home participants with mild to severe dementia. Future research should investigate different dosages and long-term treatment.


Torjesen I. Anticholinergic effects of common drugs are associated with increased mortality in over 65s. BMJ. 2011 Jun 28;342:d4037.
GERI-RXFILES DEMENTIA: COGNITIVE IMPAIRMENT REFERENCES

9. CCCDTD4
14. CCCDTD4


GERI-RXFILES DEMENTIA: BPSD REFERENCES


