DEMENTIA

BRINGING EVIDENCE & EXPERIENCE TO DRUG THERAPY DECISION POINTS

October 2014

INSIDE

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.*

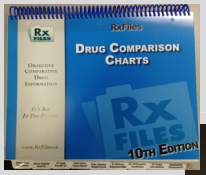
⇨*It's not easy to explain benefits & harms to patients & families.*

⇨*Current guidelines recommend a ChEI trial, but clinicians seem divided on this.*

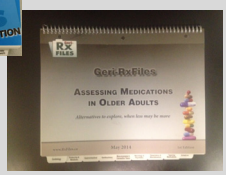
⇨*It's hard not to overestimate or underestimate concerns re: medications in dementia. A balanced approach eludes us!*

NEW AT RXFILES

RxFiles Drug Comparison Charts – 10th Edition Book – Oct 2014.



& 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

Cholinesterase Inhibitors (ChEI) for Alzheimer's Dementia	
Benefits/Advantages	**Harms/Disadvantages**
- Stabilizing or slowing progression of Alzheimer's dementia in terms of cognitive testing (modest) - *marked improvement*, uncommon, NNT=42 - *at least minimal improvement*, NNT=12 - *cognitive stabilization*, NNT=7 (Note: benefit was not noticeable to the patients taking the ChEI in trials) - Stimulating, sometimes resulting in less apathy	- Poor tolerability ◆Any adverse effect, **NNH=12** - gastrointestinal upset - increased risk of falling - urinary incontinence ◆ Stimulating, sometimes resulting in agitation or worsening of behaviour - Cost considerations - Undesirability of taking one more drug - Foster unrealistic hopes that may delay dealing with future planning
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 - 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)	- May miss out on the chance that there may be some improvement that is clinically relevant for a period of time.

⇨ 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.

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.

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.

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 Schlulich, for which we were all very grateful.

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

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!!!*

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. McLeod, Dr. B. Martens, Dr. J. Alport, Dr. V. van der Merwe, Dr. N. Olsen, Dr. K. Roelens, Dr. S. Bugden, Dr. B. Schuster, D. Bunka, A. Crawley, the families & staff at Sunnyside, & the rest of the RxFiles team. *L. Regier, J. Bareham*

A Crawley BSP, SHR Pharmacy Resident; L Regier BSP; L Kosar BSP, MSc; B Jensen BSP; J Bareham BSP MSc

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; bradycardia, 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** ARICEPT, **galantamine** REMINYL, and **rivastigmine** EXELON) 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

	Description	Evidence for ChEI (Benefits/Indications)	Cognitive Outcome
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 = 161-978 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 weeks[1] **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)
	Note: given that patients in trials were less severe with fewer co-morbidities, some expect less benefit, but more harm in *real life*.		
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.[2] 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* = 592-974 with donepezil, galantamine, & rivastigmine have shown small benefits of clinically questionable significance.[3,4]	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 .[42]	Cholinesterase inhibitors unlikely to be effective for improving cognition; may be considered for hallucinations.[2,5, 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.[46]	Cholinesterase inhibitors unlikely to be effective.

approved=official indication, Health Canada GREEN=modest benefit YELLOW=questionable benefit RED=unlikely benefit †Rivastigmine approved for **severe** in USA

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.[13;CCCDT04] **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).[8] Unfortunately, patient response cannot be predicted - other patients (~10%) will experience a rapid decline in cognitive function. {Placebo has benefit in trials!}

(See section: **When should cholinesterase inhibitors be avoided or discontinued?**)

"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.)[9]
- Despite high hopes, ChEIs have not been shown to reduce health system costs through decreasing hospitalizations or nursing home admissions. (AD2000)[10-12]

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

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***

MMSE Dementia Scoring

0-9	10-19	20-26	27-30
severe	moderate	mild	pre-clinical

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

*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://consultgerirn.org/uploads/File/trythis/try_this_d13.pdf

***Refer to **RxFiles Anticholinergics: Reference List of Drugs with Anticholinergic Effects** http://www.rxfiles.ca/rxfiles/uploads/documents/members/Psyc-anticholinergic-Ref%20List%20SPDP-complete.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

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)

Table 2: Typical Dose and Cost of Cognitive Therapy Medications

		SK/NIHB coverage?	Dose	Cost/month
Cholinesterase Inhibitors	**Donepezil** ARICEPT, g	EDS ☎ / Prior approval ✆	Initial: 5mg po daily Usual (max): 5-10mg po daily	$66 $66 (10mg)
	Galantamine REMINYL, g	EDS ☎ / Prior approval ✆	Initial: 8mg ER po daily Usual (max): 8-24mg ER po daily	$68 $68 (24mg)
	Rivastigmine EXELON, g	EDS ☎ / Prior approval ✆	Initial: 1.5mg po BID Usual (max): 1.5-6mg po BID **Patch**: 4.6mg or 9.5mg applied once daily	$70 $70 (6mg) $170
NMDA antagonist	**Memantine** EBIXA, g	*NO: ✗/⊗*	Initial: 5mg po daily Usual (max): 5-10mg po BID	$39 $67-125 (10mg)

Table 3: Cholinesterase Inhibitor Drug Interactions

	Drug			Result
	donepezil	galantamine	rivastigmine	
Pharmacodynamic				
Antipsychotics	✓	✓	✓	potential Parkinsonian symptoms
Anticholinergics	✓	✓	✓	diminished therapeutic effect
Beta-blockers	✓	✓	✓	bradycardia
Pharmacokinetic				
CYP**3A4** inhibitors (e.g. erythromycin, clarithromycin, fluconazole, ketoconazole)	✓	✓		↓ ChEI metabolism and ↑ levels
CYP**2D6** inhibitors (e.g. fluoxetine, paroxetine, quinidine)	✓	✓		
CYP inducers (e.g. rifampin, carbamazepine)	✓	✓		↑ ChEI metabolism and ↓ levels
Nicotine / Smoking			✓	

What about patients taking anticholinergics for incontinence?

Anticholinergic incontinence medications can impair cognition/cognitive performance.

- In patients with dementia, anticholinergic medications should be avoided.[36]
- In non-demented patients who are experiencing delirium from an anticholinergic (e.g. **DITROPAN**, **DETROL**, **TOVIAZ**), best practice is to discontinue the anticholinergic and use nonpharmacological therapy (moderate fluid intake, scheduled voiding, absorbent products, etc.). [A helpful guide: 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 <u>prioritize</u> 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]
- 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 **VESICARE**, darifenacin **ENABLEX**). Hydrophilic compounds have a limited ability to cross the blood brain barrier, which has lead to the development of agents such as trospium **TROSEC**. 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.[16] These drugs have not been studied in patients with dementia.
  Refer to **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.

Watch out for other causes of incontinence in the elderly[37]

- heart failure → fluid overload
- benign prostatic hyperplasia → obstruction
- constipation → fecal impaction
- immobility → increased time to reach bathroom
- urinary tract infections → urinary urgency
- medications e.g. diuretics, antipsychotics, antidepressants, sedatives

When should cholinesterase inhibitors be avoided or discontinued?

Continual assessment of patients on cholinesterase inhibitors is paramount!

- Common side effects of ChEIs are nausea[31%], vomiting[21%], dizziness[15%], diarrhea[14%], and headache[14%].[17] Behaviour disturbances may also occur. It is essential to regularly **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 in patients whose **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.[19]
- 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. Take into account the patient and patient's family's perspectives.
- If discontinuing a ChEI, a 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]

ChEI Drug Holidays?

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.[46]

✗=non-formulary Sask ⊗=not covered by NIHB ☎=Exceptional Drug Status Saskatchewan ✆=prior approval NIHB **AD**=Alzheimer's disease **ADAS-Cog**=cognitive section of the Alzheimer's Disease Assessment Scale (Scale 0-70; lower score better) **ChEI**=cholinesterase inhibitor **CNS**=central nervous system **CYP**=cytochrome P450 **EDS**=Exceptional Drug Status (SK) **FAQ**=Functional Activities Questionnaire (Scale 0-30; lower score indicates greater function) **FTD**=frontotemporal dementia **LBD**=Lewy body dementia **MMSE**=Mini Mental State Examination (Scale 0-30; higher score better) **NNH**=number needed to harm **NNT**=number needed to treat **NS**=non-significant **PD**=Parkinson's disease **RCT**=randomized controlled trial **VaD**=vascular dementia

What about memantine?

- Memantine EBIXA 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.[22] 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.[23]
- Memantine may have a lesser magnitude of effect than ChEIs.[24] It has been associated with a decrease in aggression & agitation, although this evidence is not rigorous.[25,40] 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.[26] DOMINO Memantine is not covered by the Saskatchewan Drug Plan (cost: $125/month). Memantine may be considered when ChEIs are not tolerated or are contraindicated.
- Side effects include: dizziness, drowsiness, confusion, insomnia, and headache. Caution is required if using memantine in patients with a history of heart disease due to an association with adverse CV events.

Table 4. When to consider memantine instead of a ChEI

Advantages	Disadvantages
1. Unique side effect profile. May be useful if patient experiences urinary incontinence, diarrhea, or nausea with ChEI.	1. Cost. Not covered by the SK Drug Plan under any circumstance. $125/month
2. Approved for moderate and **severe** dementia.	2. Not approved, nor effective for mild dementia.
3. **May** be helpful for patients who are aggressive, agitated.[25,40 post-hoc data only]	3. Twice daily dosing.
4. Minimal drug interactions.	4. ?Cardiovascular risk: in retrospective cohort study, found to have increased risk of MI[HR 1.33] and cardiac death[HR 1.31] compared to donepezil;[41] manufacturer reports increased rates of cardiovascular side effects[HF, HTN] versus placebo.[42]

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

There is insufficient evidence to recommend these products.[27-31,43] (see also Geri-RxFiles – Dementia and Cognitive Impairment)

Non-Pharmacological Measures for Dementia Treatment[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 ***A***ntecedents, ***B***ehaviours, & ***C***onsequences (***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!!!

----- 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.[17] Dosing donepezil at bedtime & with food may improve GI-related tolerability. If insomnia occurs, dosing may be changed to the morning.[32]
- Intolerable side effects are often best treated by decreasing the dose, switching to a different agent, or tapering & discontinuing therapy.

The Various Types of Dementia[1]

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)

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

A	P	N
Anticholinergic Medications *See Section 24 for a more complete list*	**Psychoactive Medications** (usually dose-related)	**Non-Psychoactive Medications**

Antibiotics (e.g. fluoroquinolones [ciprofloxacin], clarithromycin BIAXIN)	**N**
Anticonvulsants - could be due to drug interactions - altered pharmacokinetics can result in CNS toxicity within "normal" therapeutic range	**P**
Antidepressants (e.g. paroxetine PAXIL & TCAs) - all serotonergic agents, including TCAs & SSRIs, due to SSRI-induced hyponatremia?	**A, P**
Antiemetics / Antivertigo (e.g. dimenhydrinate GRAVOL)	**A**
Antihistamines / Antipruritics (e.g. hydroxyzine ATARAX)	**A**
Antimuscarinics (e.g. oxybutynin DITROPAN)	**A**
Antiparkinson Meds (e.g. levodopa/carbidopa SINEMET, pramipexole MIRAPEX, ropinirole REQUIP, amantadine SYMMYTREL)	**P**
Antipsychotics (e.g. olanzapine ZYPREXA, quetiapine SEROQUEL, risperidone RISPERDAL)	**A, P**
Class 1A Antiarrhythmics (e.g. disopyramide NORPACE, RYTHMODAN, quinidine, procainamide [anticholinergic], amiodarone CORDARONE)	**N**
Corticosteroids (e.g. prednisone)	**N**
Digoxin - digoxin toxicity can occur with "normal" serum digoxin concentrations	**N**
H2RAs (e.g. cimetidine TAGAMET, ranitidine ZANTAC) - ↓ renal function can ↑ adverse events	**A, N**
Hypnotics / Sedatives (e.g. benzodiazepines especially long-acting, high dose)	**P**
NSAIDs (e.g. diclofenac VOLTAREN, indomethacin)	**N**
Opioid Analgesics (e.g. codeine, oxycodone, morphine, hydromorphone, fentanyl)	**P**

- ❑ **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 or call 1-800-263-3367 (SK) for a referral form & more information

- ❑ **Encourage regular exercise & a healthy diet.**
- ❑ **Encourage cognitive activity (e.g. day programs).**
- ❑ **Address/acknowledge caregiver stress (Alzheimer Society, support groups, alternative living situations).**

Assessment of Cognitive Function [2, 3]

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	Presentation of Symptoms	MMSE Score
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.

Treatment Considerations for Dementia

Currently, there are 2 classes of medications available to help stabilize cognitive function in dementia: cholinesterase inhibitors (donepezil ARICEPT, galantamine REMINYL, rivastigmine EXELON) & a NMDA-antagonist (memantine EBIXA).

When deciding whether a medication for dementia is appropriate for a particular individual, consider: potential benefits, potential adverse events, cost, quality of life, & treatment goals.

Goal of Treatment

To improve the quality of life for the individual & caregivers, maintain optimal function & provide maximum comfort.

Potential Benefits of Treatment[4 5 6]

There is currently no cure for dementia/AD & no known treatment will stop its progression. Cholinesterase inhibitors in individuals with dementia produce, on average, small improvements in measures of cognition & activities of daily living (ADL). The impact for most individuals will be modest & temporary, with not everyone responding to treatment (NNT= 10-12 over 12-52 weeks) Meta-analysis. If benefits occur, they should be seen within 3 to 6 months.

What About the Long-Term Benefit?[7]

- Impact on long-term outcomes, disability & institutionalization, is not clear.
- **AD2000 Study**: Only nonpharmaceutical industry sponsored trial of cholinesterase inhibitors. [n=566 run-in, 486 randomized; duration up to 5 years] Found no significant benefit of donepezil compared with placebo for the two primary endpoints:
  - Entry to institutional care
  - Progression of disability

Cholinesterase Inhibitors [8]

There is no evidence that one cholinesterase inhibitor is more efficacious than the another[9] (grade 2B)

- Donepezil, galantamine, and rivastigmine appear to have similar efficacy & similar adverse effects, however independent comparative trials among the acetylcholinesterase inhibitors are lacking.

- **Donepezil** ARICEPT
  - Initial dose: 5 mg once daily. If well tolerated, ↑ dose to 10mg once daily after at least 4 to 6 weeks (maximum dose is 10 mg daily). [Dose at HS or with food.]

- **Galantamine** (ER) REMINYL
  - Initial dose: 8mg once daily in the morning, preferable with food. After 4 weeks, ↑ dose to 16mg once daily (initial maintenance dose). If initial maintenance dose is well tolerated, consider ↑ to 24mg once daily after at least 4 weeks (maximum dose is 24mg daily).

Cholinesterase Inhibitors continued [10]

- **Rivastigmine** EXELON

Oral

- Initial dose: 1.5mg BID (in the morning & at night), with food. If well tolerated, ↑ dose to 3mg BID after at least 2 to 4 weeks. If well tolerated, ↑ dose to 4.5mg BID & then to 6mg BID, after at least 2 weeks each time. If treatment is interrupted for several days, reinitiate starting dose (i.e. 1.5mg BID) & titrate as above to reduce the risk of severe vomiting & GI bleed (e.g. esophageal rupture).

Patch[11 12]

- Daily applications (placed in rotation around the back, chest or upper arm) – may be more reliable method of administration in demented patients. Dose can be ↑ every 4 weeks. If treatment is interrupted for >3 days, it should be restarted with the lowest-dose patch. Note, cost of patch is higher ($170 vs $70) than oral.

Cholinesterase Contraindications

- Uncontrolled/severe asthma or severe COPD
- Cardiac conduction adnormalities (special caution if on beta-blockers)
- Peptic ulcer disease
- Urinary obstruction
- Seizure history
- Concurrent use of anticholinergic medications (can negate any benefit)
- Angle-closure glaucoma
- Sick sinus syndrome
- Left bundle-branch block

N-methyl-D-aspartate (NMDA) Receptor Antagonist[13]

Generally better tolerated than the cholinesterase inhibitors, but is not effective in mild to moderate disease.[14]

- **Memantine** EBIXA
- Initial dose: 5 mg once daily, in the morning. If well tolerated, ↑ in weekly increments of 5mg to maintenance dose of 10mg BID.

Combination Therapy: Cholinesterase Inhibitor + Memantine

Combination therapy is rational, as the medications have different mechanisms of action, & appear to be safe, but there is insufficient evidence to recommend for or against this combination[15] (grade 2B). The evidence is conflicting. Some studies indicate that individuals with moderate to severe AD dementia (vs mild to moderate) may benefit from combination therapy [16 17 18] (DOMINO)[19]; however a systematic review that included two of these studies[20 21] concluded that the addition of memantine to an acetylcholinesterase inhibitor provides no additional benefit on cognitive, behavioural, functional, or global measures.[22]

Adding memantine to donepezil when an individual progresses to moderate to severe Alzheimer's is not likely to offer any benefit. (DOMINO)[23, 24, 25]

Potential Adverse Events Associated with Treatment[26 27 28 29 30]

Cholinesterase Inhibitors (donepezil ARICEPT, galantamine REMINYL, rivastigmine EXELON)

- 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 EBIXA

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[31]

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 (aggression, 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
- At 3 months: assess for cognitive effects – is there any benefit?
  - 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?

When Should a Cholinesterase Inhibitor be Discontinued?[32 33]

- 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.[(grade 2B)] 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)

Stopping a Cholinesterase Inhibitor

When it has been decided that treatment with a cholinesterase inhibitor 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.[34] 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. (grade 2C) [35] [36] [37] Symptoms may not be fully reversible if there is a delay in restarting pharmacotherapy.[38]

Can Dementia be Prevented? [39]

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.[40] 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.[41]

Dehydroepiandrosterone (DHEA) [42] [43] [44]

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.[45] 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? [46] - continued

Gingko [47] [48]

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 gingko & placebo groups.[49] Ginkgo biloba did **not** prevent dementia in one prospective trial [50]

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)[51], vitamin E (n = 6377, study duration nearly 10 yr)[52], folic acid (n = 24, study duration 4 wk)[53] & the omega-3 fatty acid EPA–DHA (eicosapentaenoic acid– docosahexaenoic acid; n = 302, study duration 6 mo)[54] 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.[55]
- 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.[56] [57] [58]

Modifiable Risk Factors[59]

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.

ANTICHOLINERGICS: Reference List of Drugs with Anticholinergic Effects [1, 2, 3, 4]

Julia Bareham BSP © www.RxFiles.ca Oct 2014

WHENEVER POSSIBLE, AVOID DRUGS WITH HIGH ANTICHOLINERGIC ACTIVITY IN OLDER ADULTS (>65 YEARS OF AGE)

Antibiotics

ampicillin	☑
cefoxitin χ	☑
clindamycin	☑
gentamicin (Oint & Sol'n NIHB covered)	☑
piperacillin χ ⊗	☑
vancomycin ☎ ⊗	☑

*All Available as Generic

Antidepressants

TCA

amitriptyline	Elavil	☒
clomipramine	Anafranil	☒
desipramine	Norpramin	☒
doxepin	Sinequan	☒
imipramine	Tofranil	☒
nortriptyline	Aventyl	☒

-less anticholinergic effects than amitriptyline & imipramine

trimipramine	Surmontil	☒

SSRI

citalopram ☆	Celexa	☑
escitalopram ☆	Cipralex χ ▼	☑
fluoxetine	Prozac	☑
fluvoxamine	Luvox	☑
paroxetine	Paxil	☒
sertraline ☆	Zoloft	☑

Other

bupropion ☆	Wellbutrin, Zyban	☑
desvenlafaxine	Pristiq χ ⊗	☑
duloxetine	Cymbalta	☑
maprotiline	Ludiomil	☑
mirtazapine ☆	Remeron	☑
moclobemide ☆	Manerix	☑
phenelzine	Nardil	☑
trazodone ☆	Trazorel	☑
venlafaxine ☆	Effexor	☑

In the elderly, citalopram [Celexa] & sertraline [Zoloft] are the usually preferred SSRIs.

Antiemetics/Antivertigo

dimenhydrinate	Gravol OTC	☒
meclizine	Bonamine	☒
promethazine	Phenergan OTC χ ⊗	☒
scopolamine	Transderm V OTC ⊗	☒

Antihistamines/Antipruritics

brompheniramine	cough&cold products OTC χ	☒
chlorpheniramine	Chlor-Tripolon OTC χ	☒
cyproheptadine	Periactin OTC χ ⊗	☒
dimenhydrinate	Gravol OTC	☒
diphenhydramine	Benadryl OTC χ	☒
hydroxyzine	Atarax	☒
pyrilamine	Midol, Pamprin OTC χ ⊗	☒
trimeprazine ◇	Panectyl ⊗	☒

Preferred Alternatives: **certirizine [Reactine] χ, fexofenadine [Allegra] χ, loratidine [Claritin] χ.**

Antimuscarinics

darifenacin	Enablex ☎ ✆	☒
fesoterodine	Toviaz ☎ χ	☒
flavoxate	Urispas χ	☒
mirabegron ◇	Myrbetriq χ ⊗	☒
oxybutynin	Ditropan (☎ on CR only)	☒
solifenacin	Vesicare ☎ ✆	☒
tolterodine l-tartrate	Detrol ☎ ✆	☒
trospium	Trosec ☎ ✆	☒

Antiparkinsonian

amantadine	Symmetrel	☑
benztropine mesylate	Cogentin	☒
bromocriptine	Parlodel	☑
carbidopa/levodopa ☆	Sinemet	☑
entacapone	Comtan	☑
ethopropazine	Parsitan	☒
pramipexole	Mirapex	☑
procyclidine	Kemadrin	☒
selegiline	Eldepryl ☎ ▼	☑
trihexyphenidyl	Artane	☒

Antipsychotics

aripiprazole ☆	Abilify ☎ ✆	☑
asenapine ◇	Saphris (☎-BPAD) ⊗	
chlorpromazine	Largactil	☒
clozapine	Clozaril ☎ ▼	☒
flupentixol	Fluanxol	☒
fluphenazine	Moditen	☒
haloperidol ☆	Haldol	☑
loxapine	Loxapac	☒
lurasidone ◇	Latuda χ ⊗	
methotrimeprazine	Nozinan	☒
olanzapine	Zyprexa ☎ ▼	☒
paliperidone ◇	Invega (☎⊗ on injection only)	☑
pericyazine	Neuleptil	☒
perphenazine	Trilafon	☒
pimozide	Orap	☒
pipotiazine ◇	Piportil	☑
quetiapine	Seroquel	☒
risperidone ☆	Risperdal (☎⊗ on injection only)	☑
thioproperazine ◇	Majeptil χ	☒
thiothixene	Navane	☒
trifluoperazine	Stelazine	☒
ziprasidone ☆	Zeldox ✆	☑
zuclopenthixol ◇	Clopixol ☎ ⊗	☒

Antiseizure Drugs

carbamazepine	Tegretol	☑
divalproex ☆	Epival	☑
oxcarbazepine	Trileptal ☎ ⊗	☑
valproic acid ☆	Depakene	☑

Preferred Alternatives: **divalproex [Epival], gabapentin [Neurontin], lamotrigine [Lamictal].**

Antispasmotics

dicyclomine	Formulex, Bentylol ⊗	☒
glycopyrrolate	Robinul χ ⊗	☒
hyoscine butylbromide	Buscopan ⊗	☒

Benzodiazepines

alprazolam	Xanax half-life: ~12 hr	☑
chlordiazepoxide	Librium half-life: ~100 hr ⊗	☑
clonazepam	Rivotril half-life: ~34 hr	☑
clorazepate	Tranxene half-life:~100 hr ⊗	☑
diazepam	Valium half-life: ~100 hr	☑
flurazepam	Dalmane half-life:~100 hr ⊗	☑
lorazepam ☆	Ativan half-life: ~15 hr	☑
midazolam	Versed half-life: ~3 hr χ ⊗	☑
oxazepam ☆	Serax half-life: ~8 hr	☑
temazepam ☆	Restoril half-life: ~11 hr	☑
triazolam	Halcion half-life: ~2 hr	☑

Avoid long- & ultra-short acting agents in the elderly. (Clonazepam ok, if long-acting required e.g. chronic anxiety)

Cardiovascular Agents

atenolol	Tenormin	☑
captopril	Capoten	☑
chlorthalidone	GENERIC ONLY	☑
digoxin	Lanoxin, Toloxin	☑
diltiazem ☆	Cardizem	☑
diospyramide	Rythmodan	☒
furosemide	Lasix	☑
hydralazine	Apresoline	☑
isosorbide ◇	Isordil	☑
metoprolol ☆	Lopresor	☑
nifedipine	Adalat	☑
quinidine	GENERIC ONLY χ ⊗	☑
triamterene	Dyrenium	☑

Gastrointestinal Agents

belladonna	GENERIC ONLY χ ⊗	☒
chlordiazepoxide/clidinium	Librax χ ⊗	☒
cimetidine	Tagamet	☒
dicyclomine	Bentylol ⊗	☒
diphenoxylate/atropine	Lomotil ⊗	☒
famotidine ☆	Pepcid OTC & Rx	☑
loperamide	Imodium OTC	☒
		☑ if used short term
metoclopramide	Maxeran	☑
nizatidine	Axid	☑
prochlorperazine	Stemetil	☒
		☑ if used short term
ranitidine	Zantac OTC & Rx	☑

-low anticholinergic activity if adjusted for renal function

Preferred Alternatives: **bisacodyl χ, PPIs ☎, domperidone; ranitidine if ≤150mg/day**

Immunosuppressants

azathioprine	Imuran	☑
cyclosporine	Neoral ☎ ✆	☑

Inhaled (COPD) Meds

aclidinium bromide	Tudorza Genuair χ ⊗	
ipratropium	Atrovent	☑
glycopyrronium	Seebri Breezhaler ☎ ✆	
tiotropium	Spiriva ☎ ✆	☑

To minimize systemic effecs of inhalational meds: avoid overuse, use aerochamber for ipratropium, extra caution with "mist" formulations in some countries.

Muscle Relaxants

baclofen	Lioresal (☎ on intrathecal only)	☑
cyclobenzaprine	Flexeril ☎ ✆	☒
methocarbamol	Robaxin OTC χ ⊗	☒
orphenadrine	Norflex OTC χ ⊗	☒
tizanidine	Zanaflex ☎ ✆	☒

Baclofen is the preferred agent of the above listed muscle relaxants however, it does display moderate to high anticholinergic activity.

Opioids

meperidine	Demerol *Not for chronic use ✆	☒
codeine	(☎ on controlled release only, ✆, inj & liquid)	☑
fentanyl	Duragesic ☎ ✆	☑
hydromorphone ☆	Dilaudid, Hydromorph Contin ✆ on CR only	☑
morphine ☆	Statex, M.O.S., Kadian	☑
oxycodone	Supedol, Oxy IR, OxyNeo ☎ ⊗	☑
tramadol ☆	Ultram, Ralivia, Tridural, Zytram XL χ ⊗	☑

Preferred Alternatives:
acetaminophen χ, NSAIDs (e.g. ibuprofen, naproxen)

Respiratory Meds

fluticasone/salmeterol	Advair ☎ ✆	☑
theophylline	Theolair, Uniphyl	☑

Miscellaneous

buspirone ◇	Buspar ⊗	☑
colchicine	GENERIC ONLY	☑
dipyridamole	Persantine, Aggrenox ☎ ✆	☑
ketotifen ophthalmic	Zaditor ☎ ⊗	☑
lithium	Carbolith, Duralith	☑
pancuronium	GENERIC ONLY χ ⊗	☑
warfarin ☆	Coumadin	☑

Moderate/High anticholinergic activity
Low anticholinergic activity
_____ = Possible preferred alternatives

☆ = Denotes agents with anticholinergic activity that may be better tolerated than others. Whenever possible, anticholinergic drugs should be avoided, & the preferred agents used.
◇ = Unable to confirm anticholinergic activity (**black** font)
☎ = **EDS** (exception drug status) in Saskatchewan
χ = **non-formulary** in Saskatchewan
✆ = **prior approval** NIHB ▼=covered by NIHB
⊗ = **not covered** by NIHB
AChEI = Acetylcholinesterase Inhibitor (eg. Donepezil [Aricept], galantamine [Reminyl], rivastigmine [Exelon]) ☎ ✆
CR = Controlled Release Formulation
PPI = Proton Pump Inhibitor (eg. rabeprazole)
OTC = Over-the-counter
☑ = Saskatchewan Health finds co-administration of this agent **with a AChEI acceptable**
☒ = If patient is currently on this medication, Saskatchewan Health will **NOT cover AChEI**

Dementia: Behavioural & Psychological Symptoms[1 2]

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.[3]

Common Behavioural & Psychological Symptoms of Dementia		
Aggression (both verbal & physical)*	Hostility	Psychomotor hyperactivity
Agitation	Intrusiveness	Repetitive behaviours
Anger, Irritability (screaming)	Nocturnal restlessness	Resistive (e.g. to personal care)
Apathy	Paranoid behaviours	Sexual disinhibition
Depression	Psychosis (includes hallucinations, delusions & paranoia)	Vocalizations (repetitive)
Emotional lability, Disinhibition		Wandering, Pacing
Hoarding		

*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.[4]
- 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 [5 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):

Psychological Triggers	Distress	Loss of Autonomy or Control
	Fear of Danger	Misinterpretation
	Feeling Abandoned	Paranoia

Environmental Triggers	"Bad Company" (not liking who is around)	Lack or Change of Routine
	Boredom	Loneliness
	Confusing Surroundings	Low Lighting
	Excessive Demands	Noise / Sounds / Certain Music

Medical Triggers	B12/Folic Acid Deficiency	Infection (e.g. pneumonia, UTI)
	Constipation or Fecal Impaction	Metabolic (e.g. hyponatremia)
	Hunger or Thirst	Nocturia
	Hypercalcemia	Pain*
	Hypothyroidism	Urinary Retention

*Undetected pain or discomfort are common in individuals with dementia, & is estimated to occur in up to 83% of individuals.[7] Pain is often poorly recognized & undertreated due to an individual's difficulty in communicating his/her needs.[8] Alternately, some complaints & request for analgesics could be attention seeking behaviour. See Section 22 for more information on assessing pain.

Medication Triggers ↘ Medication that must be tapered when discontinuing	Acetylcholinesterase Inhibitors ↘ (e.g. donepezil ARICEPT)	Fluoroquinolones (e.g. ciprofloxacin, norfloxacin)
	Anticholinergic Medications (see page 24A) ↘	H2 Antagonists (e.g. ranitidine, cimetidine)
	Anticonvulsants (e.g. carbamazepine, phenytoin) ↘	Lithium
	Anti-Parkinson Medications ↘ (e.g. levodopa/carbidopa SINEMET)	Opioids ↘ (e.g. codeine, morphine)
	Benzodiazepines ↘ (e.g. lorazepam ATIVAN)	Substance Abuse (e.g. alcohol, stimulants, others)
	Digoxin	Systemic Corticosteroids (especially high doses) ↘
	& many others, see RxFiles anticholinergic list.	

❑ **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-pharmacological 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).[9]

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[10]

- 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[11 12]

- 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[13]

- 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[14]

- Discontinue medications that may be contributing to the BPSD, when possible (taper or ↓ dose)

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**

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** BUSPAR: 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
  - B **Clonazepam** RIVOTRIL: 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 ↘.

Apathy[15 16]

Apathy 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** 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[17]
  - **Citalopram** 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[18, 19]
  - **Escitalopram** 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 CIPRALEX MELTZ
  - **Sertraline** ZOLOFT: 25 to 100mg daily
  - **Fluvoxamine** LUVOX: 25 to 150mg daily at bedtime (sedating, many drug interactions)
  - If possible, avoid **fluoxetine** PROZAC due its long-half life & avoid **paroxetine** 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).

Depression Continued

- **Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)**
  - **Venlafaxine** 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 SSRIs, but with more common GI events, & may ↑ blood pressure. High risk of withdrawal syndrome; gradual tapering important.

- **Tricyclic Antidepressants (TCAs)**
  - **Nortriptyline** 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** 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**
  - **Bupropion** 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** 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** MANERIX: 100mg daily to 300mg BID
    - May help with anxiety.
    - Can cause restlessness/↑ stimulation.

Notes:

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.[20]

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. [21]
- 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, & **quetiapine** SEROQUEL. **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.** [22] **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 & anti-dopaminergic 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.[23] 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. [24, 25, 26, 27]
  - Higher doses, older age, a diagnosis of dementia (especially vascular dementia), & comorbid atrial fibrillation have been noted as risk factors for stroke.[28]
  - The risk remains elevated for ~20 months after the initiation of treatment.[29]

- Possible ↑ risk of mortality[30 31 32]

  This is a somewhat controversial issue. There are limitations & potential confounders with the available data that leave us uncertain of 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.[33 34]
    - Risperidone: reference (risk = 1)
    - Olanzapine: relative risk = 1.02 (95% CI 0.92 to 1.12)[35]; no difference[36] (i.e. olanzapine & risperidone demonstrate no difference in risk of mortality)
    - Quetiapine: relative risk = 0.76 (95% CI 0.7 to 0.82)[37]; (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.[39]
    - For risperidone, the hazard ratio is 1.35 for high dose (>1mg), & 1.19 for medium dose (0.5 to 1mg) [40]
      - i.e. high dose risperidone users are at a 1.35x greater risk of mortality
    - For olanzapine, the hazard ratio is 1.26 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**).

❑ **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 taker longer.

Atypical Antipsychotics ↘

- **Risperidone** RISPERDAL: 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.[42]

- **Olanzapine** ZYPREXA: 1.25 to 7.5mg daily or divided BID
  - May be modestly effective for treating agitation, but generally not recommended in individuals with dementia.[43] Olanzapine's anticholinergic properties can be particularly problematic in older adults, also associated with rapid & significant weight gain (in some older adults), sedation, & hyperglycemia.[44]

- **Quetiapine** SEROQUEL: 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:[45]

- **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

The *What, Why & How* of Antipsychotic Tapering ↘ continued

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 [≥ 3 months] 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 = 4/2years (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
  - BPSD 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 the risk of recurrence of symptoms upon discontinuation?

The risk may be higher in individuals with previously severe symptoms &/or if discontinuation has caused recurrence before. A **slow, gradual taper** will **allow for monitoring** and early identification of the re-emergence of the BPSD (especially if risk of harm to self or others), which can be addressed by increasing the medication back up to the previously effective dose (this may be lower than the original dose). While the discontinuation of the medication may not be successful, the result may be that the individual is taking a lower dose of the medication.

How Do the Antipsychotics Compare? [46] [47]

Efficacy: risperidone has the most evidence for efficacy (aggression ≤1mg/day & psychosis ≤2mg/day).[48, 49]

Possible Adverse Events (all dose-dependent):

- **Anticholinergic & cognitive adverse events**: olanzapine, quetiapine > risperidone
- **EPS**: risperidone (↑ EPS doses >2-4mg/day) > olanzapine > quetiapine
- **QT Prolongation**: quetiapine >>> risperidone
- **Sedation**: olanzapine, quetiapine (lower doses of quetiapine are more sedating) > risperidone
- **Tardive Dyskinesia**: risperidone > olanzapine > quetiapine
- **Weight Gain**: olanzapine > quetiapine > risperidone

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 (or mood stabilizers) for agitation or aggression?[52]

There are many limitations to using valproate [Depakene] / divalproex [Epival], carbamazepine [Tegretol] or lamotrigine [Lamictal] for the treatment of BPSD:

- **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 [Aricept], galantamine [Reminyl], 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 analyses]).
  - Unlikely to help agitation & aggression (not better than placebo for agitation). [54]
  - May help in Lewy Body Dementia to decrease visual symptoms.

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

See Section 26 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 1st: redirection, distraction, avoiding stimulants
  - Limited data on drug treatment (SSRIs, antipsychotics, cholinesterase inhibitors)
    See RxFiles Hypersexuality Chart

References – Cholinesterase Inhibitors Newsletter – Oct 2014 - www.RxFiles.ca

1. Lanctôt, Krista L., et al. "Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis." *Canadian Medical Association Journal*169.6 (2003): 557-564.
2. Rolinski, Michal, et al. "Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease." *Cochrane Database Syst Rev* 3 (2012).
3. Massoud, Fadi. "Cholinesterase Inhibitors in Vascular Cognitive Impairment."*The Canadian Journal of Neurological Sciences* 40.4 (2013): 446-447.
4. Kavirajan, Harish, and Lon S. Schneider. "Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomised controlled trials." *The Lancet Neurology* 6.9 (2007): 782-792.
5. Wild, Rebecca, T. A. C. L. Pettit, and Alistair Burns. "Cholinesterase inhibitors for dementia with Lewy bodies." *Cochrane Database Syst Rev* 3.3 (2003).
6. Cholinesterase inhibitors: tremor and exacerbation of Parkinson's disease. Prescrire international [1167-7422] anonymous yr:2007 vol:16 iss:91 pg:197 -8
7. Mendez, Mario, Edward Lauterbach, and Shirlene Sampson. "An evidence-based review of the psychopathology of frontotemporal dementia: a report of the ANPA Committee on Research." *The Journal of neuropsychiatry and clinical neurosciences* 20.2 (2008): 130-149.
8. Cummings JL. Use of cholinesterase inhibitors in clinical practice: evidence-based recommendations. Am J Geriatr Psychiatry. 2003 Mar-Apr;11(2):131-45.
9. Blackburn, D. F., et al. "Do prior authorization policies discourage first-line antipsychotic use in patients newly discharged from a hospitalization for schizophrenia in Saskatchewan?." *Journal of population therapeutics and clinical pharmacology= Journal de la therapeutique des populations et de la pharamcologie clinique* 21.1 (2013): e31-7.
10. Tariot PN. Contemporary issues in the treatment of Alzheimer's disease: tangible benefits of current therapies. J Clin Psychiatry. 2006;67 Suppl 3:15-22.
11. Courtney C, Farrell D, Gray R, et al. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised doubleblind trial. Lancet. Jun 26, 2004;363(9427):2105-2115.
12. Courtney C, Farrell D, Gray R, et al.; AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet. 2004 Jun 26;363(9427):2105-15.
13. Gauthier, Serge, et al. "Recommendations of the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD4)."*Canadian Geriatrics Journal* 15.4 (2012): 120.
14. Bentué-Ferrer, Danièle, et al. "Clinically significant drug interactions with cholinesterase inhibitors." *CNS drugs* 17.13 (2003): 947-963.
15. Sink, Kaycee M., et al. "Dual Use of Bladder Anticholinergics and Cholinesterase Inhibitors: Long-Term Functional and Cognitive Outcomes."*Journal of the American Geriatrics Society* 56.5 (2008): 847-853.
16. Wiedemann, A., and P. A. Schwantes. "Antimuscarinic drugs for the treatment of overactive bladder: are they really all the same?—A comparative review of data pertaining to pharmacological and physiological aspects." *Eur J Ger*9.Suppl 1 (2007): 29-42.
17. Birks, J. "Cholinesterase inhibitors for Alzheimer's disease (Review)." (2012).
18. Small, Gary, and Bruno Dubois. "A review of compliance to treatment in Alzheimer's disease: potential benefits of a transdermal patch." *Current Medical Research and Opinion®* 23.11 (2007): 2705-2713.
19. Gaudig, M., et al. "Effects of Galantamine in Alzheimer's Disease: Double-blind Withdrawal Studies Evaluating Sustained Versus Interrupted Treatment."*Current Alzheimer Research* 8.7 (2011): 771-780.
20. Pariente, A., et al. "Effect of treatment gaps in elderly patients with dementia treated with cholinesterase inhibitors." *Neurology* 78.13 (2012): 957-963.
21. Winblad, Bengt, et al. "Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study." *The Lancet* 367.9516 (2006): 1057-1065.
22. Molino, Ivana, et al. "Efficacy of Memantine, Donepezil, or Their Association in Moderate-Severe Alzheimer's Disease: A Review of Clinical Trials." *The Scientific World Journal* 2013 (2013).
23. Mayeux, Richard. "Early Alzheimer's disease." *New England Journal of Medicine* 362.23 (2010): 2194-2201.
24. Raina, Parminder, et al. "Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline." *Annals of Internal Medicine* 148.5 (2008): 379-397.
25. Herrmann N, Gauthier S, et al. A randomized, double-blind, placebo-controlled trial of memantine in a behaviorally enriched sample of patients with moderate-to-severe Alzheimer's disease. Int Psychogeriatr. 2013 Mar 8:1-9.
26. Howard R et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. (DOMINO) N Engl J Med 2012 Mar 8; 366:893.
27. Tabet N, Birks J, Grimley Evans J. Vitamin E for Alzheimer's disease. Cochrane Database Syst Rev. 2000;(4):CD002854.
28. Malouf R, Areosa Sastre A. Vitamin B12 for cognition. Cochrane Database Syst Rev. 2003;(3):CD004326.
29. Lim WS, Gammack JK, Van Niekerk J, Dangour AD. Omega 3 fatty acid for the prevention of dementia. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD005379.
30. Snitz Beth E.; O'Meara Ellen S.; Carlson Michelle C.; et al. for the Ginkgo Evaluation of Memory (GEM) Study Investigators. Ginkgo biloba for Preventing Cognitive Decline in Older Adults: A Randomized Trial. JAMA. 2009;302(24):2663-2670.
31. McGuinness B, O`Hare J, Craig D, et al. Statins for the treatment of dementia. Cochrane Database Syst Rev. 2010 Aug 4;8:CD007514.
32. Seltzer, Ben. "Donepezil: a review." (2005): 527-536.
33. Spijker, Anouk, et al. "Effectiveness of Nonpharmacological Interventions in Delaying the Institutionalization of Patients with Dementia: A Meta-Analysis."*Journal of the American Geriatrics Society* 56.6 (2008): 1116-1128.
34. Douglas, Simon, Ian James, and Clive Ballard. "Non-pharmacological interventions in dementia." *Advances in Psychiatric Treatment* 10.3 (2004): 171-177.
35. Curyo K, Ogland-Hand S. 2013 Webinar Series. State of the Science: Dementia Evaluation and Management among Diverse Older Adults and their Families. Non-pharmacological interventions for persons with dementia & behaviour problems. Accessed from http://sgec.stanford.edu/webinar/2013Handouts/Curyto_Ogland-Hand_3-20-2013_SGEC-2perpage.pdf September 15 2014.
36. Hogan, David B., et al. "Management of mild to moderate Alzheimer's disease and dementia." *Alzheimer's & Dementia* 3.4 (2007): 355-384.
37. Ballert, Katie N., and Gregory T. Bales. "Dementia and Overactive Bladder."*Current Bladder Dysfunction Reports* 8.1 (2013): 57-61.
38. Jewart, Rita D., et al. "Cognitive, behavioral, and physiological changes in Alzheimer disease patients as a function of incontinence medications." *The American journal of geriatric psychiatry* 13.4 (2005): 324-328.
39. Lipton, Richard B., Ken Kolodner, and Keith Wesnes. "Assessment of cognitive function of the elderly population: effects of darifenacin." *The Journal of urology*173.2 (2005): 493-498.
40. Wilcock, Gordon K., et al. "Memantine for agitation/aggression and psychosis in moderately severe to severe Alzheimer's disease: a pooled analysis of 3 studies." *The Journal of clinical psychiatry* 69.3 (2008): 341-348.
41. Fosbøl, Emil L., et al. "Comparative Cardiovascular Safety of Dementia Medications: A Cross-National Study." *Journal of the American Geriatrics Society* 60.12 (2012): 2283-2289.
42. Memantine monograph. Accessed from https://www.lundbeck.com/upload/ca/en/files/pdf/product_monograph/EBIXA_PM_MKT_ctrl_138778_eng_v2_20Apr2011.pdf September 17, 2014
43. Vellas, Bruno, et al. "Long-term use of standardised Ginkgo biloba extract for the prevention of Alzheimer's disease (GuidAge): a randomised placebo-controlled trial." *The Lancet Neurology* 11.10 (2012): 851-859.
44. McKeith, Ian, et al. "Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study." *The Lancet*356.9247 (2000): 2031-2036.
45. Mori, Etsuro, Manabu Ikeda, and Kenji Kosaka. "Donepezil for dementia with Lewy bodies: A randomized, placebo-controlled trial." *Annals of neurology* 72.1 (2012): 41-52.
46. Kerchner, Geoffrey A., Maria Carmela Tartaglia, and Adam L. Boxer. "Abhorring the vacuum: use of Alzheimer's disease medications in frontotemporal dementia." *Expert review of neurotherapeutics* 11.5 (2011): 709-717.
47. Lee, Joyce, et al. "The use of a cholinesterase inhibitor review committee in long-term care." *Journal of he American Medical Directors Association* 8.4 (2007): 243-247.

GERI-RXFILES ANTICHOLINERGIC REFERENCES

---

[1] Carnahan RM, Lund BC, Perry PJ, et al. The Anticholinergic Drug Scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. J Clin Pharmacol. 2006 Dec;46(12):1481-6.

[2] National Prescribing Service. Examples of medications with anticholinergic activity. January 2009. Available: http://www.brisbanesouth.com.au/content/Document/Resources/NPS/NPS%20Anticholinergic%20Medications%20200902.pdf

[3] Chew ML, Mulsant BH, Pollock BG, et al. Anticholinergic activity of 107 medications commonly used by older adults. J Am Geriatr Soc. 2008 Jul;56(7):1333-41.

[4] Mintzer J, Burns A. Anticholinergic side-effects of drugs in elderly people. J R Soc Med. 2000 Sep;93(9):457-62.

[5] Feinberg M. The problems of anticholinergic adverse effects in older patients. Drugs Aging. 1993 Jul-Aug;3(4):335-48.

[6] Tune LE. Anticholinergic effects of medication in elderly patients. J Clin Psyc. 2001.

[7] Treatment of Dry Mouth. Canadian Pharmacist's Letter 2010; 26(10):261006.

[8] Drugs with Anticholinergic Activity. Canadian Pharmacist's Letter 2011; 27(12):271206.

ADDITIONAL REFERENCES

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

Campbell NL, Boustani MA, Lane KA, et al. Use of anticholinergics and the risk of cognitive impairment in an African American population. Neurology. 2010 Jul 13;75(2):152-9.

Carrière I, Fourrier-Reglat A, Dartigues JF, et al. Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: the 3-city study. Arch Intern Med. 2009 Jul 27;169(14):1317-24.

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.

Kennedy J, Deberdt W, Siegal A, et al. **Olanzapine does not enhance cognition** in non-agitated and non-psychotic patients with mild to moderate Alzheimer's dementia. Int J Geriatr Psychiatry. 2005 Nov;20(11):1020-7.

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.

Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. Arch Intern Med. 2008 Mar 10;168(5):508-13.

Sink KM, Thomas J 3rd, Xu H, Craig B, et al. Dual Use of Bladder Anticholinergics and Cholinesterase Inhibitors: Long-Term Functional and Cognitive Outcomes. J Am Geriatr Soc. 2008 Apr 1. [Epub ahead of print] In higher-functioning NH residents, dual use of ChIs and bladder anticholinergics may result in greater rates of functional decline than use of ChIs alone. The MDS-COGS may not be sensitive enough to detect differences in cognition due to dual use.

Teramura-Grönblad M, Muurinen S, Soini H, et al. Use of anticholinergic drugs and cholinesterase inhibitors and their association with psychological well-being among frail older adults in residential care facilities. Ann Pharmacother. 2011 May;45(5):596-602.

The American Geriatrics Society **2012 Beers Criteria Update** Expert Panel. American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2012 Feb 29.

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

---

[1] Davidson M, Thorpe L, Bareham J. An Introduction to the Various Types of Dementia, Their Management & Treatment. April 2014.
[2] Kurlowitz, L, & Wallace, M. (Jan 1999). Try This: Best practices in nursing care to older adults: The mini mental state examination (MMSE), Issue #3. Retrieved June 6, 2004, from The John A. Hartford Foundation Institute for Geriatric Nursing, College of Nursing, New York University
[3] Durso SC, Sullivan GM, eds. *Geriatrics Review Syllabus: A Core Curriculum in Geriatric Medicine*. 8th ed. New York: American Geriatrics Society; 2013.
[4] Hogan DB, Bailey P, Black S, Carswell A, Chertkow H, Clarke B, Cohen C, Fisk JD, Forbes D, Man-Son-Hing M, Lanctôt K, Morgan D, Thorpe L. Diagnosis and treatment of dementia: 5. Nonpharmacologic and pharmacologic therapy for mild to moderate dementia. CMAJ. 2008 Nov 4;179(10):1019-26.
[5] Qaseem A, Snow V, Cross JT Jr, et al. Current pharmacologic treatment of dementia: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med 2008;148:370-8.
[6] AAGP position statement: principles of care for patients with dementia resulting from Alzheimer disease. http://www.aagponline.org/index.php?src=news&submenu=Tools_Resources&srctype=detail&category=Position%20Statement&refno=35.
[7] AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet 2004; 363: 2105-2115.
[8] Hogan DB, Bailey P, Black S, Carswell A, Chertkow H, Clarke B, Cohen C, Fisk JD, Forbes D, Man-Son-Hing M, Lanctôt K, Morgan D, Thorpe L. Diagnosis and treatment of dementia: 5. Nonpharmacologic and pharmacologic therapy for mild to moderate dementia. CMAJ. 2008 Nov 4;179(10):1019-26.
[9] CCCDTD4
[10] Hogan DB, Bailey P, Black S, Carswell A, Chertkow H, Clarke B, Cohen C, Fisk JD, Forbes D, Man-Son-Hing M, Lanctôt K, Morgan D, Thorpe L. Diagnosis and treatment of dementia: 5. Nonpharmacologic and pharmacologic therapy for mild to moderate dementia. CMAJ. 2008 Nov 4;179(10):1019-26.
[11] AWentrup et al. Once-daily transdermal rivastigmine in the treatment of Alzheimer's disease. Drug Des Devel Ther 2008; 2:245.
[12] J Cummings et al. Randomized, double-blind, parallel-group, 48-week study for efficacy and safety of a higher-dose rivastigmine patch (15 vs 10 cm2) in Alzheimer's disease. Dement Geriatr Cogn Disord 2012; 33:341.
[13] Hogan DB, Bailey P, Black S, Carswell A, Chertkow H, Clarke B, Cohen C, Fisk JD, Forbes D, Man-Son-Hing M, Lanctôt K, Morgan D, Thorpe L. Diagnosis and treatment of dementia: 5. Nonpharmacologic and pharmacologic therapy for mild to moderate dementia. CMAJ. 2008 Nov 4;179(10):1019-26.
[14] Herrmann N, Chau SA, Kircanshi I, Lanctot KL. Current and emerging drug treatment options for Alzheimer's disease: a systematic review. Drugs 2011;71:2031-65.
[15] CCCDTD4
[16] PN Tariot et al. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA 2004; 291:317.
[17] GT Grossberg et al. The safety, tolerability and efficacy of once-daily memantine (28 mg): A multinational, randomized, double-blind, placebo-controlled trial in patients with moderate-to-severe Alzheimer's disease taking cholinesterase inhibitors. CNS Drugs 2013; 27:469.
[18] AP Porsteinsson et al. Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomized, double blind, placebo-controlled trial. Curr Alzheimer Res 2008; 5:83.
[19] R Howard et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease (**DOMINO**). N Engl J Med 2012; 366:893.
[20] Tariot PN, Farlow MR, Grossberg GT, et al. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: randomized controlled trial. JAMA 2004;291:317-24.

[21] Porsteinsson AP, Grossberg GT, Mintzer J, et al. Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomized, double-blind, placebo-controlled trial. Curr Alzheimer Res 2008;5:83-9.
[22] Peninsula Medical School. Universities of Exeter and Plymouth. Peninsula Technology Assessment Group (PenTAG). The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of TA111): a systematic review and economic model. June 18, 2010. http://www.nice.org.uk/nicemedia/live/12248/49789/49789.pdf.
[23] R Howard et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease (**DOMINO**). N Engl J Med 2012; 366:893.
[24] Peninsula Medical School. Universities of Exeter and Plymouth. Peninsula Technology Assessment Group (PenTAG). The effectiveness and cost effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of TA111): a systematic review and economic model. June 18, 2010. http://www.nice.org.uk/nicemedia/live/12248/49789/49789.pdf.
[25] PL Detail-Document, Pharmacotherapy and Advancing Alzheimer's Disease. Pharmacist's Letter/Prescriber's Letter. May 2012.
[26] Hogan DB, Bailey P, Black S, Carswell A, Chertkow H, Clarke B, Cohen C, Fisk JD, Forbes D, Man-Son-Hing M, Lanctôt K, Morgan D, Thorpe L. Diagnosis and treatment of dementia: 5. Nonpharmacologic and pharmacologic therapy for mild to moderate dementia. CMAJ. 2008 Nov 4;179(10):1019-26.
[27] Pharmacotherapy choices for patients with dementia. Pharmacist's Letter/Prescriber's Letter 2008;24(5):240510.
[28] Gill SS, Anderson GM, Fischer HD, Bell CM, Li P, Normand ST, Rochon PA. Syncope and its' consequences in patients with dementia receiving cholinesterase inhibitors: a population based cohort study. Arch Intern Med. 2009;169(9):867–73.
[29] Gill SS, Anderson GM, Fischer HD, Bell CM, Li P, Normand ST, Rochon PA. Syncope and its' consequences in patients with dementia receiving cholinesterase inhibitors: a population based cohort study. Arch Intern Med. 2009;169(9):867–73.
[30] Hernandez RK, Farwell W, Cantor MD, Lawler EV. Cholinesterase inhibitors and incidence of bradycardia in patients with dementia in the Veterans Affairs New England Healthcare System. J Am Geriatr Soc. 2009;57:1997–2003.
[31] Lanctôt KL, Herrmann N, Yau KK, et al. Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis. CMAJ 2003; 169:557.
[32] Moore A, Patterson C, Lee L, Vedel I, Bergman H. Fourth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia: recommendations for family
physicians. Can Fam Physician. 2014 May;60(5):433-8.
[33] PL Detail-Document, Pharmacotherapy and Advancing Alzheimer's Disease. Pharmacist's Letter/Prescriber's Letter. May 2012.
[34] Howard R, McShane R, Lindesay J, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. N Engl J Med 2012;366:893-903.
[35] Overshott R, Burns A. Treatment of dementia. J Neurol Neurosurg Psychiatry 2005;76(Suppl 5):53-9.
[36] Singh S, Dudley C. Discontinuation syndrome following donepezil cessation. Int J Geriatr Psychiatry2003;18:282-4.
[37] Kwak YT, Han IW, Suk SH, Koo MS. Two cases of discontinuation syndrome following cessation of memantine. Geriatr Gerontol Int 2009;9:203-5.
[38] Kwak YT, Han IW, Suk SH, Koo MS. Two cases of discontinuation syndrome following cessation of memantine. Geriatr Gerontol Int 2009;9:203-5.
[39] Naqvi R, Liberman D, Rosenberg J, Alston J, Straus S. Preventing cognitive decline in healthy older adults. CMAJ. 2013 Jul 9;185(10):881-5.
[40] . Martin BK, Szekely C, Brandt J, et al. Cognitive function over time in the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT). *Arch Neurol* 2008;65:896-905.
[41] Cooper C, Li R, Lyketsos C, Livingston G. Treatment for mild cognitive impairment: systematic review. Br J Psychiatry. 2013 Sep;203(3):255-64.
[42] Wolf OT, Neumann O, Hellhammer DH, et al. Effects of a two week physiological DHEA substitution on cognitive performance and well-being in healthy elderly women and men. J Clin Endocrinol Metab 1997;82:2363-7.
[43] van Niekerk JK, Huppert FA, Herbert J. Salivary cortisol and DHEA: association with measures of cognition and well-being in normal older men, and effects of three months of DHEA supplementation. Psychoneuroendocrinology 2001;26:591-612.

[44] Kritz-Silverstein D, von Muhlen D, Laughlin GA, et al. Effects of DHEA supplementation on cognitive function and quality of life. J Am Geriatr Soc 2008;56:1292-8.
[45] Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, et al; WHIMS Investigators. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in Postmenopausal women: the Women's Health Initiative Memory Study: a randomized Controlled trial. JAMA. 2003;289:2651-62.
[46] Naqvi R, Liberman D, Rosenberg J, Alston J, Straus S. Preventing cognitive decline in healthy older adults. CMAJ. 2013 Jul 9;185(10):881-5.
[47] Solomon PR, Adams F, Silver A, et al. Ginkgo for memory enhancement. *JAMA* 2002;288:835-40.
[48] Dodge HH, Zitzelberger T, Oken BS, et al. A randomized placebo-controlled trial of Ginkgo biloba for the prevention of cognitive decline. *Neurology* 2008;70:1809-17.
[49] Dodge HH, Zitzelberger T, Oken BS, et al. A randomized placebo-controlled trial of Ginkgo biloba for the prevention of cognitive decline. *Neurology* 2008;70:1809-17.
[50] DeKosky ST, Williamson JD, Fitzpatrick AL, Kronmal RA, Ives DG, Saxton JA, et al; Ginkgo Evaluation of Memory (GEM) Study Investigators.Ginkgo biloba for prevention of dementia: a randomized controlled trial. JAMA. 2008;300:2253-62.
[51] Deijen JB, van der Beek EJ, Orlebeke JF, et al. Vitamin B-6 supplementation in elderly men: effects on mood, memory, performance and mental effort. Psychopharmacology (Berl) 1992; 109: 489-96
[52] Kang JH, Cook N, Manson J, et al. A randomized trial of vitamin E supplementation and cognitive function in women. Arch Intern Med 2006;166:2462-8.
[53] Pathansali R, Mangoni AA, Creagh-Brown B, et al. Effects of folic acid supplementation on psychomotor performance and hemorheology in healthy elderly subjects. Arch Gerontol Geriatr 2006; 43:127-37.
[54] van de Rest O, Geleijnse JM, Kok FJ, et al. Effect of fish oil on cognitive performance in older subjects. *Neurology* 2008; 71: 430-8.
[55] Cassilhas RC, Viana VA, Grassmann V, et al. The impact of resistance exercise on the cognitive function of the elderly. *Med Sci Sports Exerc* 2007;39:1401-7.
[56] Willis SL, Tennstedt SL, Marsiske M, et al. Long-term effects of cognitive training on everyday functional outcomes in older adults. *JAMA* 2006;296:2805-14.
[57] Smith GE, Housen P, Yaffe K, et al. A cognitive training program based on principles of brain plasticity: results from the improvement in memory with plasticity-based adaptive cognitive training (IMPACT) study. *J Am Geriatr Soc* 2009;57:594-603.
[58] Berry AS, Zanto TP, Clapp WC, et al. The influence of perceptual training on working memory in older adults. *PLoS ONE* 2010;5:e11537.
[59] Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol. 2011;10:819-28.

GERI-RXFILES DEMENTIA: BPSD REFERENCES

[1] American Geriatrics Society. Geriatrics Evaluation & Management Tools. New York: American Geriatrics Society; 2013.
[2] RxFiles. Management of Behavioural & Psychological Symptoms of DEMENTIA (BPSD). 2011. Available: http://www.rxfiles.ca/rxfiles/uploads/documents/Psych-BPSD-Newsletter.pdf
[3] http://www.bpac.org.nz/a4e/resources/docs/bpac_A4E_best_practice_guide.pdf
[4] British Columbia Ministry of Health. Best Practice Guideline for Accommodating and Managing Behavioural and Psychological Symptoms of Dementia in Residential Care: A Person-Centered Interdisciplinary Approach. 2012. Available: http://www.health.gov.bc.ca/library/publications/year/2012/bpsd-guideline.pdf
[5] Drouillard ND, Mithani A, Chan PKY. Therapeutic approaches in the management of behavioral and psychological symptoms of dementia in the elderly. BCMJ. 2013 Mar 2013;55(2):90-95.
[6] Davidson M, Thorpe L, Bareham J. An introduction to the various types of dementia, their management & treatment. RxFiles. 2014.
[7] Shipton EA. Pain assessment in dementia. N Z Med J 2008;121(1286):9–11.
[8] http://www.bpac.org.nz/a4e/resources/docs/bpac_A4E_best_practice_guide.pdf
[9] Sadowsky CH, Galvin JE. Guidelines for the management of cognitive and behavioral problems in dementia. J Am Board Fam Med. 2012 May-Jun;25(3):350-66.
[10] American Geriatrics Society. Geriatrics Evaluation & Management Tools. New York: American Geriatrics Society; 2013.
[11] American Geriatrics Society. Geriatrics Evaluation & Management Tools. New York: American Geriatrics Society; 2013.
[12] http://www.bpac.org.nz/a4e/resources/docs/bpac_A4E_best_practice_guide.pdf
[13] American Geriatrics Society. Geriatrics Evaluation & Management Tools. New York: American Geriatrics Society; 2013.
[14] American Geriatrics Society. Geriatrics Evaluation & Management Tools. New York: American Geriatrics Society; 2013.
[15] Dolder CR, Davis LN, McKinsey J. Use of psychostimulants in patients with dementia. Ann Pharmacother. 2010 Oct;44(10):1624-32.
[16] Davidson M, Thorpe L, Bareham J. An introduction to the various types of dementia, their management & treatment. RxFiles. 2014.
[17] PL Detail-Document, Pharmacotherapy of Dementia Behaviors. Pharmacist's Letter/Prescriber's Letter. October 2011.
[18] PL Detail-Document, Pharmacotherapy of Dementia Behaviors. Pharmacist's Letter/Prescriber's Letter. October 2011.
[19] Porsteinsson AP, Drye LT, Pollock BG, Devanand DP, Frangakis C, Ismail Z, Marano C, Meinert CL, Mintzer JE, Munro CA, Pelton G, Rabins PV, Rosenberg PB, Schneider LS, Shade DM, Weintraub D, Yesavage J, Lyketsos CG; CitAD Research Group. Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. JAMA. 2014 Feb 19;311(7):682-91.
[20] Moore A, Patterson C, Lee L, Vedel I, Bergman H. Fourth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia: recommendations for family physicians. Can Fam Physician. 2014 May;60(5):433-8.
[21] Ballard CG, Waite J, Birks J. Atypical antipsychotics for aggression and psychosis in Alzheimer's disease: Review. Cochrane Database of Systematic Reviews 2006; Issue 1.
[22] Moore A, Patterson C, Lee L, Vedel I, Bergman H. Fourth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia: recommendations for family physicians. Can Fam Physician. 2014 May;60(5):433-8.
[23] Mittal V, Kurup L, Williamson D, Muralee S, Tampi RR. Risk of cerebrovascular adverse events and death in elderly patients with dementia when treated with antipsychotic medications: a literature review of evidence. Am J Alzheimers Dis Other Demen. 2011 Feb;26(1):10-28.

[24] Herrmann N, Lanctôt KL. Do atypical antipsychotics cause stroke? CNS Drugs. 2005;19(2):91-103.
[25] Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. Am J Geriatr Psychiatry. 2006 Mar;14(3):191-210.
[26] Ballard CG, Waite J, Birks J. Atypical antipsychotics for aggressions and psychosis in Alzheimer's disease (Review). *Cochrane Database Syst Rev.* 2009;4:1-128.
[27] Maher AR, Maglione M, Bagley S, Suttorp M, Hu JH, Ewing B, Wang Z, Timmer M, Sultzer D, Shekelle PG. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. JAMA. 2011 Sep 28;306(12):1359-69.
[28] Mittal V, Kurup L, Williamson D, Muralee S, Tampi RR. Risk of cerebrovascular adverse events and death in elderly patients with dementia when treated with antipsychotic medications: a literature review of evidence. Am J Alzheimers Dis Other Demen. 2011 Feb;26(1):10-28.
[29] Mittal V, Kurup L, Williamson D, Muralee S, Tampi RR. Risk of cerebrovascular adverse events and death in elderly patients with dementia when treated with antipsychotic medications: a literature review of evidence. Am J Alzheimers Dis Other Demen. 2011 Feb;26(1):10-28.
[30] Mittal V, Kurup L, Williamson D, Muralee S, Tampi RR. Risk of cerebrovascular adverse events and death in elderly patients with dementia when treated with antipsychotic medications: a literature review of evidence. Am J Alzheimers Dis Other Demen. 2011 Feb;26(1):10-28.

- Schneider LS, Tariot PN, Dagerman KS, Davis SM, Hsiao JK, Ismail MS, Lebowitz BD, Lyketsos CG, Ryan JM, Stroup TS, Sultzer DL, Weintraub D, Lieberman JA; CATIE-AD Study Group. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. N Engl J Med. 2006 Oct 12;355(15):1525-38.
- De Deyn PP, Rabheru K, Rasmussen A, Bocksberger JP, Dautzenberg PL, Eriksson S, Lawlor BA. A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. Neurology. 1999 Sep 22;53(5):946-55.
- Ballard C, Hanney ML, Theodoulou M, Douglas S, McShane R, Kossakowski K, Gill R, Juszczak E, Yu LM, Jacoby R; DART-AD investigators. The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial. Lancet Neurol. 2009 Feb;8(2):151-7.
- Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. Am J Geriatr Psychiatry. 2006 Mar;14(3):191-210.

[31] The place of antipsychotics in the treatment of the behavioural and psychological symptoms of dementia Available: http://www.bpac.org.nz/a4e/bpacGuide.asp
[32] Kales HC, Kim HM, Zivin K, Valenstein M, Seyfried LS, Chiang C, Cunningham F, Schneider LS, Blow FC. Risk of mortality among individual antipsychotics in patients with dementia. Am J Psychiatry. 2012 Jan;169(1):71-9.
[33] Kales HC, Kim HM, Zivin K, Valenstein M, Seyfried LS, Chiang C, Cunningham F, Schneider LS, Blow FC. Risk of mortality among individual antipsychotics in patients with dementia. Am J Psychiatry. 2012 Jan;169(1):71-9.
[34] Huybrechts KF, Gerhard T, Crystal S, Olfson M, Avorn J, Levin R, Lucas JA, Schneeweiss S. Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study. BMJ. 2012 Feb 23;344:e977.
[35] Kales HC, Kim HM, Zivin K, Valenstein M, Seyfried LS, Chiang C, Cunningham F, Schneider LS, Blow FC. Risk of mortality among individual antipsychotics in patients with dementia. Am J Psychiatry. 2012 Jan;169(1):71-9.
[36] Huybrechts KF, Gerhard T, Crystal S, Olfson M, Avorn J, Levin R, Lucas JA, Schneeweiss S. Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study. BMJ. 2012 Feb 23;344:e977.
[37] Kales HC, Kim HM, Zivin K, Valenstein M, Seyfried LS, Chiang C, Cunningham F, Schneider LS, Blow FC. Risk of mortality among individual antipsychotics in patients with dementia. Am J Psychiatry. 2012 Jan;169(1):71-9.

[38] Huybrechts KF, Gerhard T, Crystal S, Olfson M, Avorn J, Levin R, Lucas JA, Schneeweiss S. Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study. BMJ. 2012 Feb 23;344:e977.
[39] Huybrechts KF, Gerhard T, Crystal S, Olfson M, Avorn J, Levin R, Lucas JA, Schneeweiss S. Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study. BMJ. 2012 Feb 23;344:e977.
[40] Huybrechts KF, Gerhard T, Crystal S, Olfson M, Avorn J, Levin R, Lucas JA, Schneeweiss S. Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study. BMJ. 2012 Feb 23;344:e977.
[41] Huybrechts KF, Gerhard T, Crystal S, Olfson M, Avorn J, Levin R, Lucas JA, Schneeweiss S. Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study. BMJ. 2012 Feb 23;344:e977.
[42] The place of antipsychotics in the treatment of the behavioural and psychological symptoms of dementia Available: http://www.bpac.org.nz/a4e/bpacGuide.asp
[43] The place of antipsychotics in the treatment of the behavioural and psychological symptoms of dementia Available: http://www.bpac.org.nz/a4e/bpacGuide.asp
[44] The place of antipsychotics in the treatment of the behavioural and psychological symptoms of dementia Available: http://www.bpac.org.nz/a4e/bpacGuide.asp
[45] The place of antipsychotics in the treatment of the behavioural and psychological symptoms of dementia Available: http://www.bpac.org.nz/a4e/bpacGuide.asp
[46] CATIE-AD - Schneider LS, Tariot PN, Dagerman KS, Davis SM, Hsiao JK, Ismail MS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. NEJM 2006; 355:1525-1538.
[47] RxFiles Chart ANTIPSYCHOTICS (AP): Frequently Asked Questions Available: http://www.rxfiles.ca/rxfiles/uploads/documents/members/Cht-Psyc-Neuroleptics.pdf
[48] Schneider LS, Tariot PN, Dagerman KS, Davis SM, Hsiao JK, Ismail MS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. NEJM 2006; 355:1525-1538. CATIE-AD
[49] Gauthier S, Cummings J, Ballard C, Brodaty H, Grossberg G, Robert P, Lyketsos C. Management of behavioral problems in Alzheimer's disease. Int Psychogeriatr. 2010;22:346-72.
[50] The place of antipsychotics in the treatment of the behavioural and psychological symptoms of dementia Available: http://www.bpac.org.nz/a4e/bpacGuide.asp
[51] PL Detail-Document, Pharmacotherapy of Dementia Behaviors. Pharmacist's Letter/Prescriber's Letter. October 2011.
[52] PL Detail-Document, Pharmacotherapy of Dementia Behaviors. Pharmacist's Letter/Prescriber's Letter. October 2011.
[53] Moore A, Patterson C, Lee L, Vedel I, Bergman H. Fourth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia: recommendations for family physicians. Can Fam Physician. 2014 May;60(5):433-8.
[54] Howard RJ, Juszczak E, Ballard CG, Bentham P, Brown RG, Bullock R, Burns AS, Holmes C, Jacoby R, Johnson T, Knapp M, Lindesay J, O'Brien JT, Wilcock G, Katona C, Jones RW, DeCesare J, Rodger M; CALM-AD Trial Group. Donepezil for the treatment of agitation in Alzheimer's disease. N Engl J Med. 2007 Oct 4;357(14):1382-92.
[55] Herrmann N, Gauthier S, et al. A randomized, double-blind, placebo-controlled trial of memantine in a behaviorally enriched sample of patients with moderate-to-severe Alzheimer's disease. Int Psychogeriatr. 2013 Mar 8:1-9.
[56] Wilcock, Gordon K., et al. "Memantine for agitation/aggression and psychosis in moderately severe to severe Alzheimer's disease: a pooled analysis of 3 studies." *The Journal of clinical psychiatry* 69.3 (2008): 341-348.