Aggression at the LTC/Tertiary Level

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Learning Objectives

1. Distinguish the different manifestations of behavioural and psychological symptoms of dementia (BPSD)

2. Discuss the framework around treating BPSD as recommended through a recent Canadian BPSD management guideline

3. Summarize the different categories of pharmacotherapies for agitation and aggression in BPSD

Disclosure for Dr. Chan

- **Relationships with commercial interests related to the topic:**
  - **none**
- **Including:**
  - **Grants/Research Support: none**
  - **Speakers Bureau/Honoraria: none**
  - **Ad Board/Consulting Fees: none**
  - **Investments or Shares: none**
  - There will be discussion of off-label uses of psychotropic medications

Mitigating Potential Bias

- Use of generic names for medications
- Review of various classes of pharmacological agents, and not focusing on just a one class

Prevalence and Incidence of Dementia in Canada: 2022-2023

Age Group	65-79	80+	90+	Total
Dementia Prevalence	138,255	348,730	135,470	622,455
Dementia Prevalence Rate	2.37%	17.24%	29.04%	8.7%
Incidence Rate of Dementia (per 100,000)	610	3669	6189	10,468

Does not include prevalence and incidence age < 65 yrs old

Source: Canadian Chronic Disease Surveillance System, Gov. of Canada

Rios *et al. BMC Geriatrics* (2017) 17:244
DOI 10.1186/s12877-017-0636-8

BMC Geriatrics

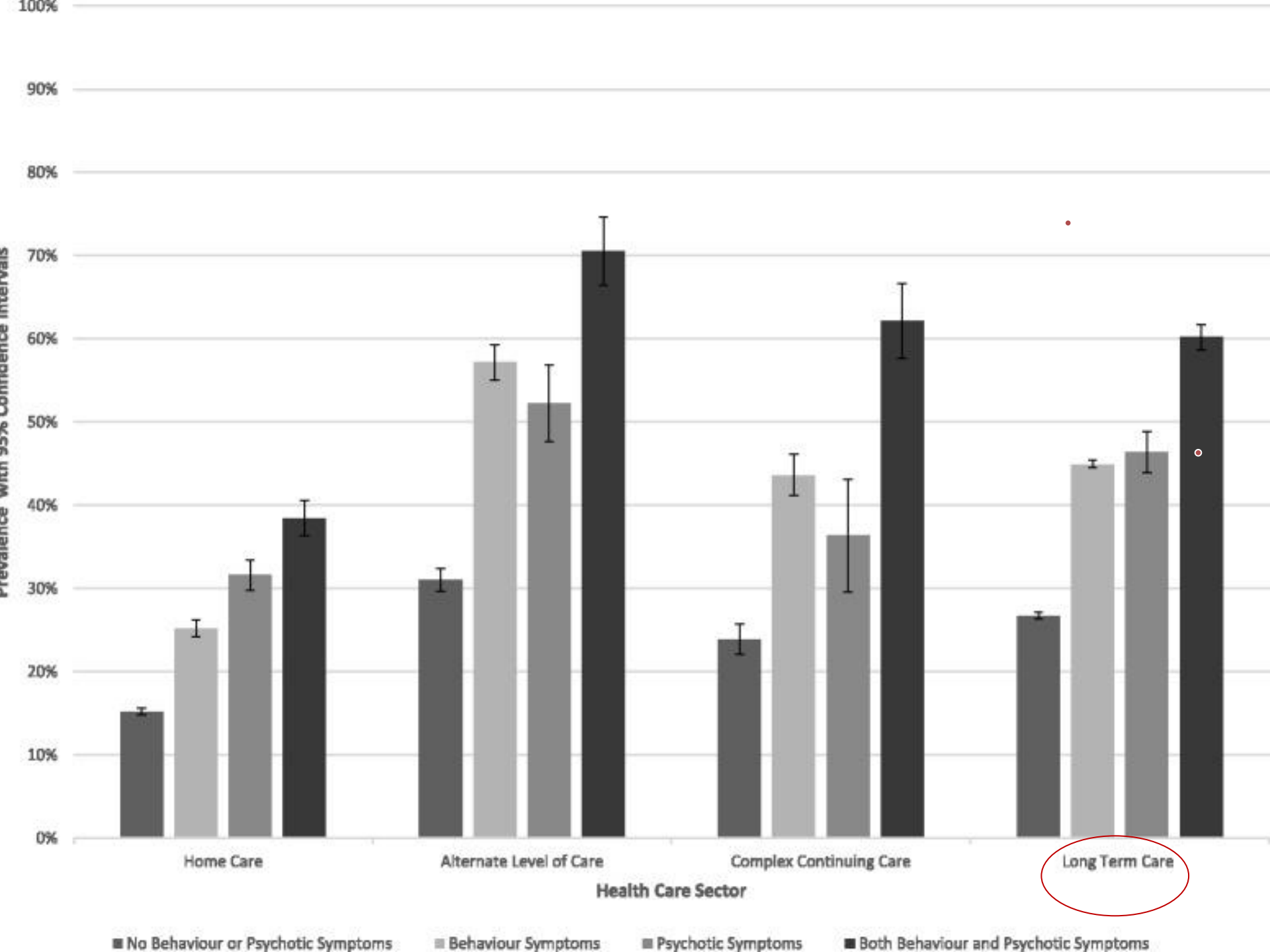
RESEARCH ARTICLE Open Access

Antipsychotics and dementia in Canada: a retrospective cross-sectional study of four health sectors

Sebastian Rios[1], Christopher M. Perlman[1*], Andrew Costa[2,3], George Heckman[1,2], John P. Hirdes[1] and Lori Mitchell[4]

Abstract

Background: Antipsychotic medications are not recommended for the management of symptoms of dementia, particularly among persons with no behavioral or psychological symptoms. We examine patterns of antipsychotic medication use among persons with dementia across health sectors in Canada, with a focus on factors related to


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Prevalence with 95% Confidence Intervals
Home Care
Alternate Level of Care
Complex Continuing Care
Long Term Care
Health Care Sector
No Behaviour or Psychotic Symptoms
Behaviour Symptoms
Psychotic Symptoms
Both Behaviour and Psychotic Symptoms

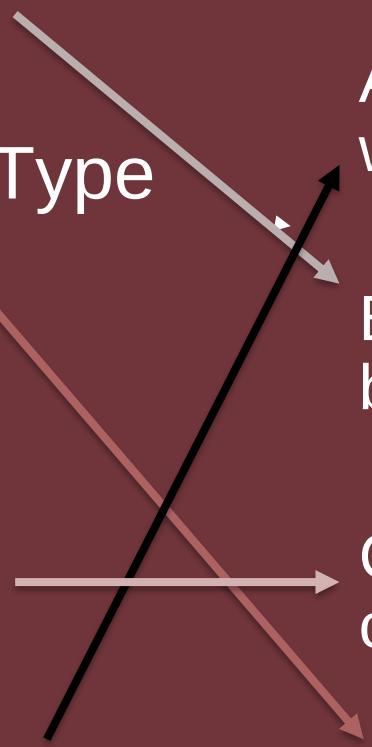
Dementia subtypes

1. Frontotemporal Type (bvFTD)

2. Lewy Body Type (LBD)

3. Parkinson's Disease (PDD)

4. Alzheimer's Type (AD)



A. Most common in pop. with dementia <age 65

B. Presents initially with behavioural issues

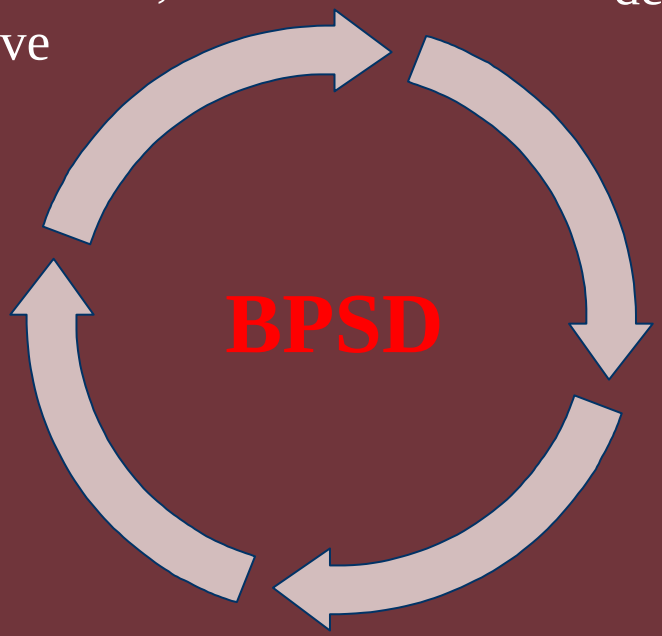
C. Visual misperceptions common

D. Visual hallucinations common

BPSD? NPS?

- DSM 5:
  - “Major NeurocognitiveDisorder”=Dementia
  - “Mild Neurocognitive Disorder”=Mild Cognitive Impairment=MCI
- BPSD/NPS
  - NPS= neuropsychiatric symptoms= BPS
  - 75% prevalence in community seniors + dementia
  - Multiple domains, may be concurrent and overlapping
  - Can occur at any stage of the disease
  - Not specific to a subtype of Dementia

BPSD Clusters



Apathy

Absence of responsiveness; lack of initiative

Psychosis

delusion, hallucination

Aggression/Agitation

verbal, physical; agitation = verbal or motor inappropriate response, not due to needs or confusion

Affective

dysphoria, elation irritability, anxiety

Hyperactivity

pacing, restlessness, disinhibition

Around 90% of those with dementia develop BPSD during course of illness

Case #1-part 1

- 83 yo man, resides in LTC home. Advanced dementia, urinary incontinence usual, ambulatory with walker. Irritable and unprovoked striking out in common areas.
- Much more aggression during care, requiring multiple staff members to assist, as striking out has led to staff injuries. Not sleeping well, nightmares reported but could be nocturnal visual hallucinations

Differential Diagnosis

- Delirium
  - Acute change, fluctuation. CAM to screen
  - "DIMS-R" (constipation, urinary retention)
    - Chan, BCMJ, vol. 53 , No. 8 , October 2011
- Depression in Dementia
  - Difficult to diagnose esp advance dementia
  - Expanded definition, use of CSDD tool
  - CCSMH BPSD National Guidelines 2014, 2024: citalopram, escitalopram, *sertraline, bupropion, mirtazapine, *duloxetine, venlafaxine

*first line agents for geriatric depression, CCSMH Depression Guide 2021

Delirium, Dementia, Lewy Body Dementia: Cole Am J Geri P 2004

Feature	Delirium	Alzheimer's	Lewy Body Dis
Onset	Acute	Insidious	Insidious
Duration	Hours, Days	Months, Years	Months, Years
Consciousness	Variably alert	Alert	Alert
Attention	Impaired	Intact	Frequently impaired
Cognitive Fluc.	Frequent	Infrequent	Frequent
Symptom Fluc.	Frequent	Infrequent	Infrequent
Visual Hallucinate	Frequent, transient	Occasional	Frequent, complex, persistent
Thinking	Disorganized	Impoverished	Impoverished
Insight	May be present in lucid intervals	Usually absent	Usually absent
Parkinsonism	Usually absent	Occasional	Frequent
Neuroleptic sensitivity	Infrequent	Infrequent	Frequent
EEG	Marked slowing	Usually normal or mild slowing	Can show slowing

Pain in Those with Dementia

- Pain (Flo, Drugs and Aging 2014; Binnekade Pain Med 2017)
  - Under-detected
  - Verbal vs. non-verbal cues
  - observed prevalence of pain for: AD (34.4%) and Mixed Dementia (34.0%)

4 B's of discomfort in older adults with dementia. Harris , BMJ 2011

Bowels: when was the patient's last bowel movement

Bladder: when did they last urinate? Any urinary symptoms?

Beverage: are they thirsty or hungry?

Bottom (to Top): Visual survey for obvious precipitants of distress and agitation

Treating Pain Husebo 2011, Husebo 2014

- Stepwise protocol for treatment of pain over 8 weeks in LTC residents with moderate-severe Dementia can:
  - Improve agitation
  - Improve mood
  - Improve apathy
  - Improve night-time behaviours
  - Improve appetite

  *Did not improve ADLs or cognition
- Stepwise protocol initiated if pain identified:

1. Acetaminophen plain (up to 3 g/day)
2. Oral morphine (up to 20mg/day)—Substitute hydromorphone?
3. Transdermal buprenorphine—Substitute oxycodone, fentanyl?
4. Pregabalin—Substitute gabapentin?

BRITISH COLUMBIA

Best Practice Guideline for Accommodating and Managing Behavioural and Psychological Symptoms of Dementia in Residential Care

A Person-Centered Interdisciplinary Approach

October 25, 2012

Management of BPSD

- Non-pharmacological Approach =
  - P.I.E.C.E.S model
    - P = Physical
    - I = Intellectual
    - E = Emotional
    - C = Capabilities
    - E = Environment
    - S = Social
  - BC BPSD project: http://www.bcbpsd.ca
- Pharmacological

BPSD and Response to Meds

Usually Not Respond to Medications

Simple Wandering

Inappropriate urination/defecation

Inappropriate dressing/undressing

Disruptive repetitive activities (perseveration) or vocalizations

Tugging at lapbelts

Hiding / hoarding

Can Be Responsive to Medications

Anxiety

Sadness, crying, sleep complaints and other depressive symptoms

Withdrawal and apathy

Elation, pressured speech and hyperactivity (manic-like)

Persistent and distressing delusions or hallucinations

Physical aggression or persistent verbal aggression

Sexually inappropriate behaviour

Sleep disturbance

Pharmacotherapy for BPSD

- Atypical Antipsychotics (AP's)
  - Risperidone, Olanzapine, Quetiapine
  - Aripriprazole, Brexpiprazole
  - Clozapine
- Typical Antipsychotics
- Antidepressants: SSRI's
- Anticonvulsants
- Benzodiazepines
- Cannabis, Cannabinoids

Antidepressants for agitation and psychosis in Dementia. (Seitz et al. 2013, Cochrane Database; Barak 2011, CCSMH BPSD Guidelines 2024)

- Citalopram, Escitalopram
  - Agitation, anxiety, irritability, depressive symptoms (not MDD), disinhibition
  - "Psychosis of Moderate Severity": some evidence for citalopram[1] and escitalopram[2] in RCTs compared with risperidone.
  - CCSMH 2024: "we suggest against using.." other SSRI's, TCA's, trazodone

- Evidence for SSRI effectiveness for BPSD in bvFTD esp. for disinhibition, irritability, aggression, and aberrant motor activity[3]

1=Pollock 2007; 2=Barak 2011; 3=Nisar 2021

SSRI's Side effects

- Interaction with Warfarin, Digoxin, Statins, ß-Blockers and Calcium channel blockers via cytochrome P450 system
- Hyponatremia (SIADH) particularly in the elderly
- Risk of falls, fractures, and osteoporosis
- Risk of GI bleed doubled esp. with NSAID's, warfarin
- FDA warning (2011): ↑QT_c for Citalopram >40mg/d
- Health Canada (2012): For elderly, max dose 20 mg/d Citalopram and 10 mg/d Escitalopram.

NOTE: (1) Baseline Na level, Na within 4 weeks
(2) Carefully monitor INR's if on warfarin
(3) Consider baseline ECG

Case #1-part 2

- Non-pharmacological measures, analgesics, melatonin 6 mg qhs, mirtazapine 15 mg qhs and citalopram at 20 mg/d have no appreciable effect on BPSD. Sleep seems worse.

Pharmacotherapy for BPSD

- Atypical Antipsychotics (AP's)
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- Typical Antipsychotics
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- Antidepressants
- Cannabis, Cannabinoids

Antipsychotics are indicated when:

- there is a ***significant risk of harm*** to the patient or others **or**
- when agitation or aggressive symptoms are
  - ***persistent,***
  - ***recurrent, or***
  - ***severe enough***

  to cause significant suffering and distress, or significant interference with care

Salzman et al 2008; CCSMH 2024;GPAC 2008;Lyketsos et al 2006

Examples of Commonly Used Antipsychotic Dosages for the BPSD

(Drouillard, Mithani, Chan. BCMJ, vol. 55 , No. 2 , March 2013)

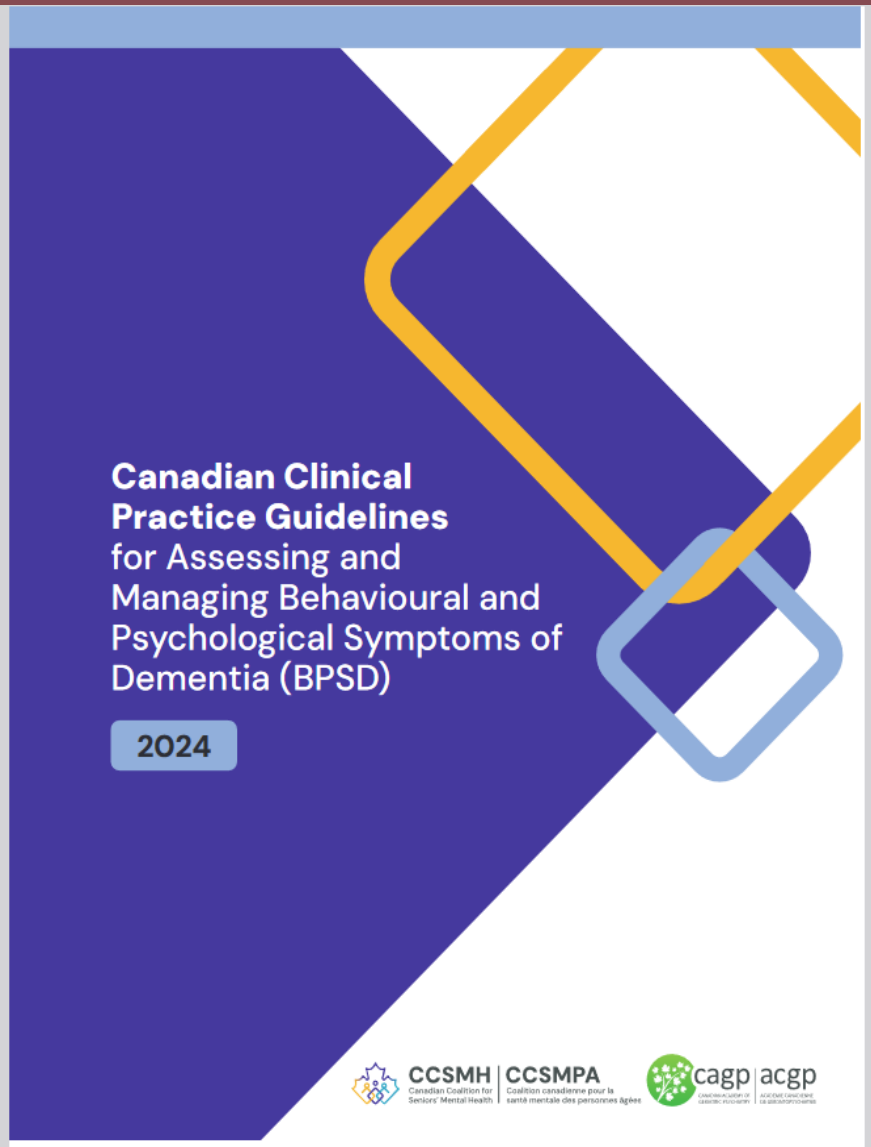
Medication	Starting Dose (mg)	Dosing Frequency	Incremental Dose (mg)	Average Total Daily Dose (mg)
quetiapine	12.5	bid/tid/hs (if XR)	12.5-25	150
risperidone	0.25	od/bid	0.25	1
olanzapine	1.25	od (hs)/bid	1.2-2.5	5
loxapine	2.5	bid/tid	2.5-5	25
haloperidol	0.25	od/bid	0.25-0.5	2
aripiprazole	0.5	od	0.5-1	2-10

Avoid Risperidone, Olanzapine and Loxapine in Lewy Body Dementia (LBD) or Parkinson's Disease Dementia (PDD). Haloperidol contraindicated.

Case #1-part 3

- After successful management with Loxapine 15 mg/d and supplemented with Quetiapine prn’s over 2 weeks, he develops a gait disturbance and begins to lean to the right when upright.

www.ccsmh.ca (2024 BPSD CPGs)



Antipsychotics for Severe Agitation in BPSD

- "We suggest aripiprazole, brexpiprazole or risperidone for the treatment of severe agitation in Alzheimer's disease and related dementia. (Conditional, moderate-quality evidence)"-- aripiprazole or risperidone if just psychosis (first line)
- "We suggest quetiapine…if symptoms are refractory to other pharmacological treatments, or in cases where other treatments are not tolerated due to extrapyramidal side-effects. (Conditional, low-quality evidence)"—may use typicals if refractory to these
- "We suggest against using olanzapine…except short-term emergency use" (strong recommend)

Antipsychotics for BPSD in PDD or LBD

- LTC Guidelines, 2014 "..appropriate pharmacological treatment of residents with behavioural symptoms or psychosis associated with Parkinson's disease dementia (PDD) or Dementia with Lewy bodies (LBD) includes:
  - a) cholinesterase inhibitors; or as a last resort
  - b) an atypical antipsychotic with less risk of exacerbating extrapyramidal symptoms, (eg: quetiapine)."

*Clozapine, aripiprazole, brexpiprazole otherwise

Atypical Antipsychotics: Mortality Risk (Black Box Warning in 2005 by Health Canada)

- Mortality risk
  - Odds Ratio= 1.7 times
    (FDA April 2005)
    - 17 studies: 5106 pts, 4.5% vs 2.6% placebo
  - Odds Ratio= 1.54 times
    (Schneider JAMA 2005;294:15)
    - 15 studies: 3353 pts, 3.5% vs 2.3% placebo

Bannerjee, S. The use of antipsychotic medication for people with dementia: Time for action. Report to UK Dept of Health, 2009

- “15 randomised placebo-controlled trials of atypical antipsychotics provides robust evidence for an increased risk of CVAEs, with a pooled relative risk of 2.57 (95% CI 1.41-4.66)”

- Base rate is less than 5%
- Health Canada Feb 2015: Risperidone restricted only to severe Alzheimer’s dementia due to risk of CVAEs

Atypical AP's and side effects

- Risperidone, Olanzapine
  - EPS, Gait disturbance
  - Infection risk (UTI, URTI)
  - Peripheral edema (Risperidone), orthostasis (Risperidone)
  - Metabolic syndrome, wt gain uncommon
- Quetiapine
  - Orthostasis, sedation
  - Prolong QTc
  - Agitation, insomnia (norquetiapine)
- Aripiprazole
  - Insomnia, akathisia-like, least QTc

General Considerations

- NNT for benefit: 5 - 14 patients
- NNH for mortality: 100 patients

So…1 death for every 9 – 25 who benefit

Get consent from SDM

Withdraw gradually within 3-6 months once BPSD stabilized (see BPSD guide)

Case #1-part 4

- With the diagnosis of probable Lewy Body Dementia, he stabilized on quetiapine, donepezil, and mirtazapine
- However, even though he is calm through most of the day and sleeps well, he is still a 3 person assist during personal care with verbal and physical aggression

Pharmacotherapy for BPSD

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- Typical Antipsychotics
- Antidepressants: SSRI's
- Anticonvulsants/Benzo's (Others)
- Cannabis, Cannabinoids

Anticonvulsants and Benzo's

- Anticonvulsants (2024 CCSMH Guide):
  - Not recommend valproic acid
  - Modest recommendation for carbamazepine
  - Gabapentinoids: esp neuropathic pain
- Benzodiazepines
  - Short-acting much preferred such as lorazepam or alprazolam.
  - Recommend only for short-term treatment on urgent basis if danger to self or others, and other unavailable or contraindicated

Treating Aggression with Personal Care

- Address situational issues
- Pharmacological options (prn's):
  - Ultra-brief-acting: sufentanil sublingual
  - Medium-acting: loxapine, methotrimeprazine
  - Longer-acting: zuclopenthixol IM (24-72 hr)
  - Very long-acting: antipsychotic IM depot—not recommended in 2024 BPSD guide unless there is established co-occurring psychotic disorder and other measures have failed (eg: aripiprazole, risperidone, paliperidone, zuclopenthixol depot)

Pharmacotherapy for BPSD

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- Typical Antipsychotics
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- Anticonvulsants/Benzo's
- Cannabis, Cannabinoids


Study : More senior citizens using pot...
REALLY FEELING MY JOINTS TODAY...
ME, TOO!
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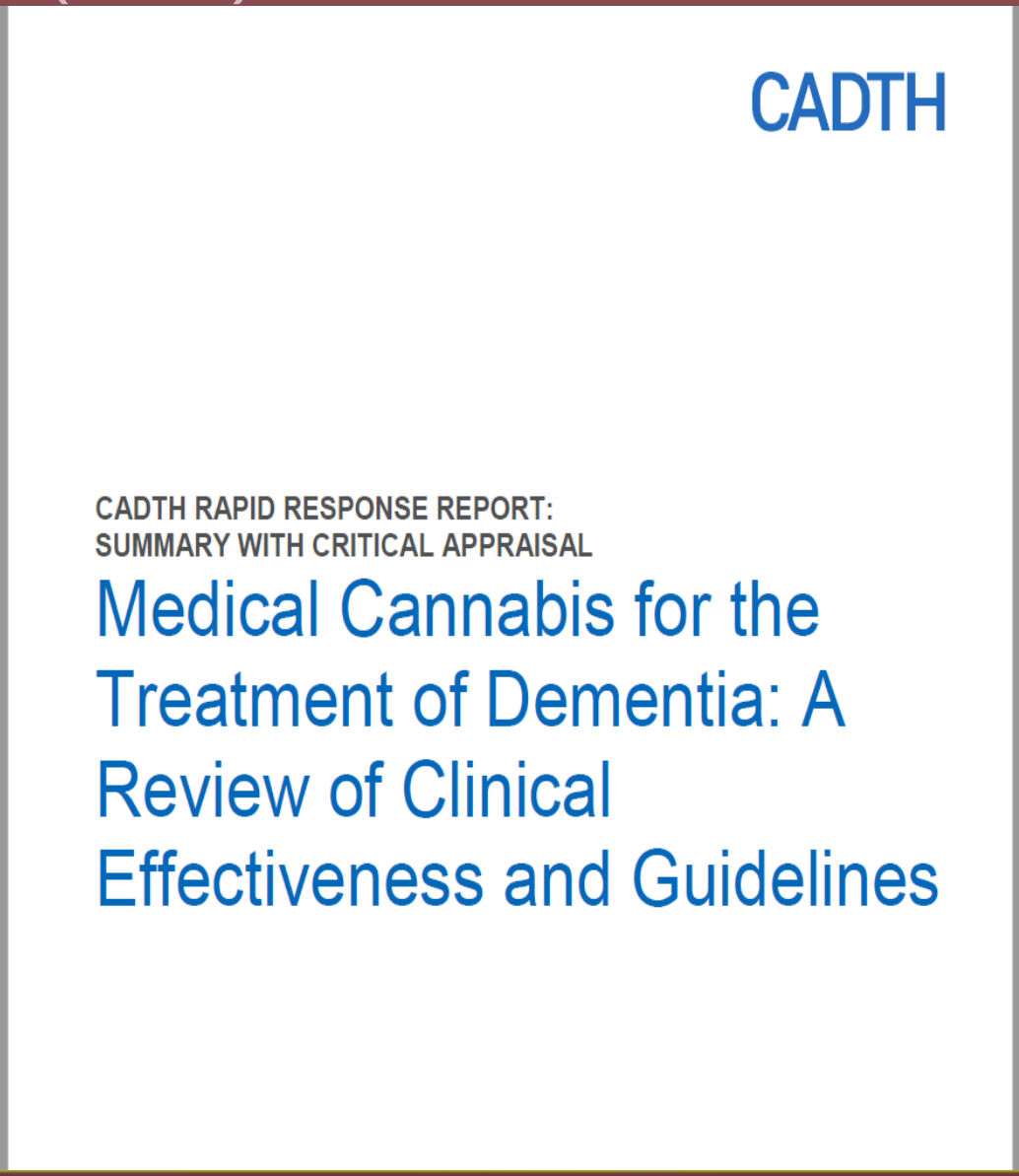
Canadian Agency for Drug and Technologies in Health (2019)



Systematic Reviews

- CADTH: “limited evidence…suggested that medical cannabis may be effective for NPS in dementia, ie: agitation, disinhibition, irritability, aberrant motor behaviour, nocturnal behaviour disorders, and aberrant vocalization and resting care.”

- Clin Gerontology (2021): Findings from a few robust RCTs suggest that nabilone might be useful for the treatment of agitation in patients with dementia, but there is no convincing evidence for THC.

Cannabis and Cannabinoids (www.rxfiles.ca)

- Smoking MJ: not usually recommended
- Dronabinol (5 mg/d) and Purified oral THC (1.5 – 4.5 mg/d): lack of availability in Canada
- Oral THC/CBD (1:25) oil: 0.2 ml bid starting
- Pure CBD oil: 100 mg/ml (<0.009 mg/ml THC)
- Nabilone: start 0.25 mg od po, then bid-qid. Maximum dose 4-6 mg per day. Go slow

Nabilone: synthetic cannabinoid

- Partial agonist CB_1 and CB_2 receptors
- Resembles THC in effect, anti-inflame
- Half-life: 2 hrs. Absorption peak: 2hrs
- Moderate CYP450 2C8/2C9 inhibitor

- S/E: drowsiness, dry mouth, dizziness, vertigo, ataxia, psychiatric symptoms. Can elevate supine and standing heart rates and cause postural hypotension.
- Aim for 1 mg qid in refractory BPSD

Take Home Points

- Consider stepwise approach to pain, if at all suspected, especially in advanced dementia
- SSRI's are possible alternatives to antipsychotics but have risks associated
- Antipsychotics for aggression and psychosis, but substitute decision-maker consent for longer term use
- Medical cannabis and cannabinoids are emerging options but limited evidence

Online Resources

- BPSD tools: www.bcbpsd.ca
- BPSD Best Practices Guidelines in BC (2012)
  - www.health.gov.bc.ca/library/publications/year/2012/bpsd-guideline.pdf
- CCSMH BPSD Practice Guidelines (2024). www.ccsmh.ca
- Drouillard, Mithani, Chan “Therapeutic approaches in the management of BPSD in the elderly” BCMJ, vol. 55 , No. 2 , March 2013