Choosing Wisely:

When Psychosis Isn't the Diagnosis

November 16, 2019

Presenter Disclosure

- Presenter: **Samantha Yau**

- I have no current or past relationships with commercial entities

Commercial Support Disclosure

- This program has received no financial or in-kind support from any commercial or other organization

Learning Objectives

- Apply the Choosing Wisely: Antipsychotic Recommendations
- Discuss the literature of antipsychotics for BPSD & Insomnia
- Provide an approach designed to help with the management of responsive behaviours of dementia, with a focus on antipsychotic medications

Choosing Wisely Recommendations

- **Don’t use antipsychotics as first choice to treat behavioural and psychological symptoms of dementia.**
- **Don’t prescribe antipsychotic medications for behavioural and psychological symptoms of dementia (BPSD) in individuals with dementia without an assessment for an underlying cause of the behavior.**
- **Don’t routinely use antipsychotics to treat primary insomnia in any age group. Question the use of antipsychotics as a first-line intervention to treat primary insomnia in any age group.**
- **Avoid use of hypnotics as primary therapy for chronic insomnia in adults; instead offer cognitive-behavioral therapy, and reserve medication for adjunctive treatment when necessary.**
- **Don’t continue medications that are no longer indicated or where the risks outweigh the benefits.**

https://www.choosingwisely.org/clinician-lists/

Growing Concerns

- Overuse of antipsychotics in older adults
- $75 million spent on antipsychotic prescriptions dispensed in Canada second quarter of 2015
- Increase in prescriptions of 32% in 4-year span
- 22.4% of residents in Canadian LTC homes in 2014 were taking antipsychotics chronically

Bjerre L et al Canadian Family Physician January 2018

Case

BY, 65 y/o male with vascular dementia with multiple admissions to the hospital. BY has suffered from 2 major cerebral hemorrhages (2015 and 2017)

CC: patient is experiencing poor sleep & agitation and aggression

Past Medical History:
Cerebral Myeloid Angiopathy and Vascular Dementia
Epilepsy
Right shoulder pain x years
Hypertension
Skin Lesions (back)
Depression x 10 years
Constipation

Case (cont'd)

Med	Dose	Sig	Route
Acetaminophen Tab	500 mg	QID	PO
Amlodipine Besylate	10 mg	Once daily	PO
Bisacodyl	10 mg	QDinner	PO
Carbamazepine	400 mg	Q12	PO
Clonazepam	2 mg	QAM	PO
Clonazepam	2 mg	QPM	PO
Gabapentin	900 mg	QHS	PO
Gabapentin	300 mg	0830, 1200	PO
Hydromorphone HCL	0.5 mg	Q4H/PRN	PO
Lactulose	30 G	BID/PRN	TOP
Lorazepam	1-2 mg	Q4H/PRN	PO/SL
Melatonin	9 mg	2000	SL
Methotrimeprazine	25 mg	0600, 1200, 1700, 2100	PO
Mirtazapine	45 mg	QHS	PO
Quetiapine	150 mg	0830, 1200, 1700	PO
Quetiapine	50 mg	0600	PO
Zopiclone	5 mg	2000	PO

Major Adverse Outcomes with antipsychotics over 6-12 weeks

- Parkinsonism
- Sedation
- Gait disturbance
- Increased respiratory infections
- Oedema
- Accelerated cognitive decline
- Stroke (>3 fold)
- Other thromboembolic events
- Mortality (1.5-1.7 fold)

Schneider et al 2005,Ballard et al 2009

Deprescribing antipsychotics for behavioural and psychological symptoms of dementia and insomnia

Evidence-based clinical practice guideline

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Figure 1

October 2016

Antipsychotic (AP) Deprescribing Algorithm

Why is patient taking an antipsychotic?

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

Recommend Deprescribing

Strong Recommendation (from Systematic Review and GRADE approach)

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

Stop AP
Good practice recommendation

Continue AP
or consult psychiatrist if considering deprescribing

Monitor every 1-2 weeks for duration of tapering

Expected benefits:

- May improve alertness, gait, reduce falls, or extrapyramidal symptoms

Adverse drug withdrawal events (closer monitoring for those with more severe baseline symptoms):

- Psychosis, aggression, agitation, delusions, hallucinations

If BPSD relapses:

Consider:

- Non-drug approaches (e.g. music therapy, behavioural management strategies)

Restart AP drug:

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

Alternate drugs:

- Consider change to risperidone, olanzapine, or aripiprazole

If insomnia relapses:

Consider

- Minimize use of substances that worsen insomnia (e.g. caffeine, alcohol)
- Non-drug behavioural approaches (see reverse)

Alternate drugs

- Other medications have been used to manage insomnia. Assessment of their safety and effectiveness is beyond the scope of this deprescribing algorithm. See AP deprescribing guideline for details.

Bjerre LM, Farrell B, Hogel M, Graham L, Lemay G, McCarthy L, et al. Deprescribing antipsychotics for behavioural and psychological symptoms of dementia and insomnia. Evidence-based clinical practice guideline. *Can Fam Physician* 2018;64:17-27 (Eng), e1-12 (Fr).

deprescribing.org

INSTITUT DE RECHERCHE Bruyère RESEARCH INSTITUTE

open

Potential Barriers to Deprescribing

Non-pharmacologic alternatives:

- limited access
- highly resource dependent
- requiring additional staff training

Bjerre L et al. Canadian Family Physician 2018

Deprescribing APs vs Continuous AP Benefits vs Harms

DART-AD

Objective:

- Assess whether continued treatment with antipsychotics in people with AD is associated with an increased risk of mortality

Study Design:

- Randomised, placebo-controlled, parallel, two-group treatment discontinuation trial
- N=165 (Age 67–100)
- Enrolled patients with AD who resided in Care facilities in the UK over 3 year period
- Patients either continued their AP treatment (thioridazine, chlorpromazine, haloperidol, trifluoperazine or risperidone) for 12 months or to switch to oral placebo

Primary Outcome:

- Mortality at 12 months

Ballard et al. Lancet Neurology 2009

DART-AD: Results

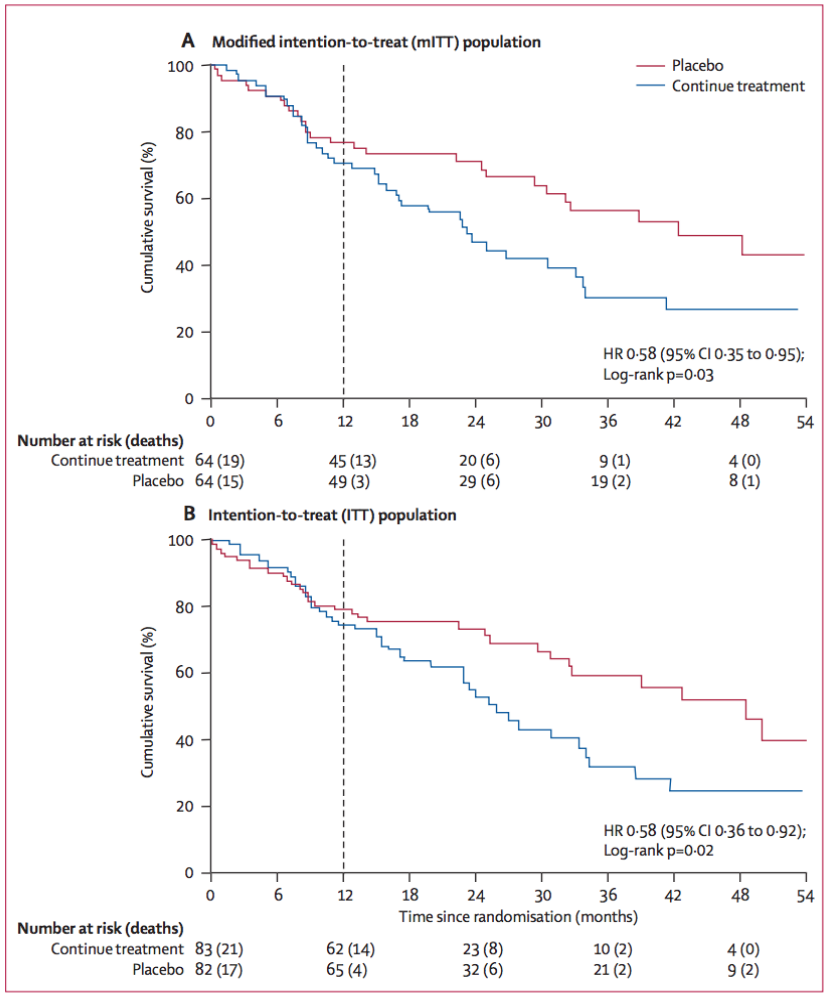


Figure 2: **Kaplan–Meier survival estimates**
The broken vertical line indicates the end of the 12-month randomised trial.

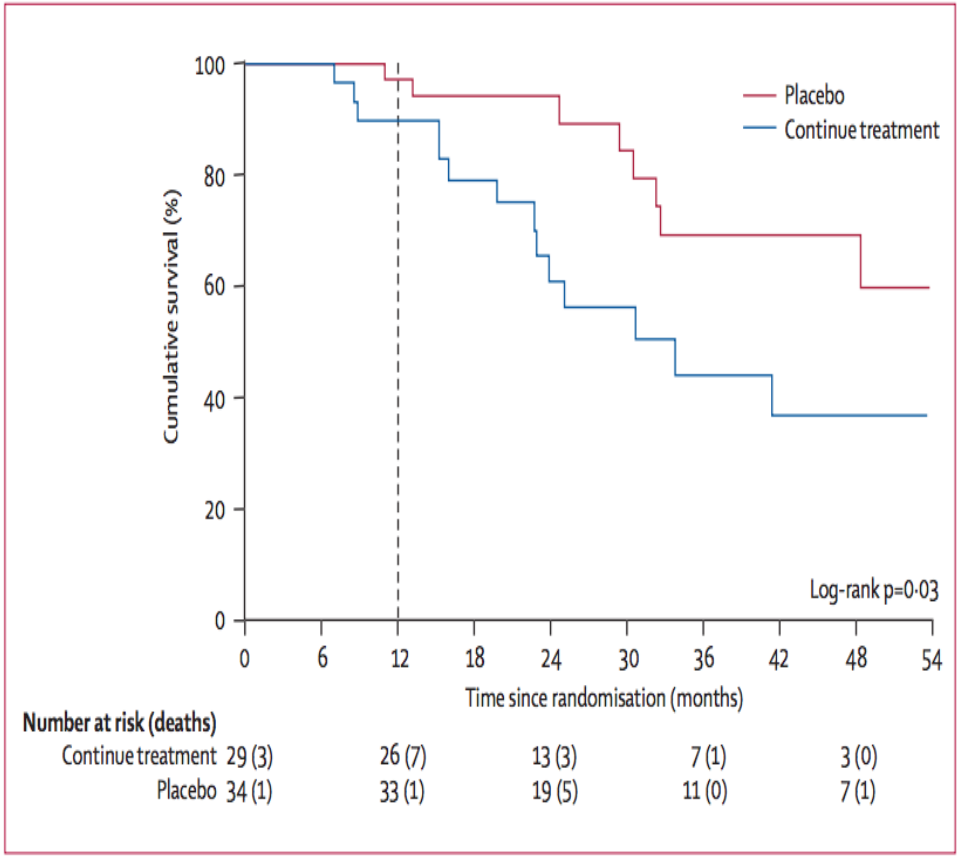
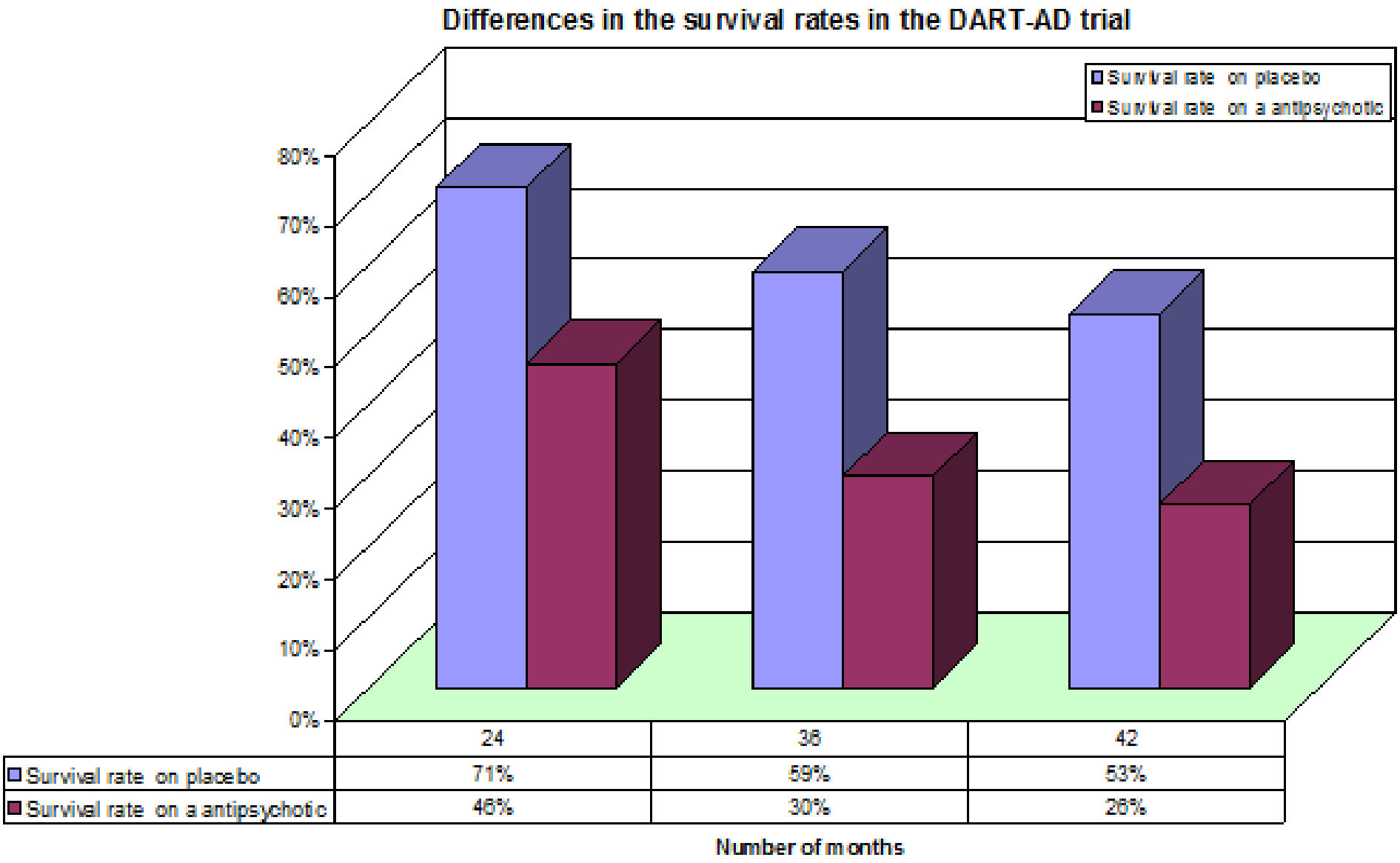


Figure 3: **Kaplan–Meier survival estimates of participants who received at least one dose of treatment and continued allocated treatment for 12 months**
The broken vertical line indicates the end of the 12-month randomised trial.

DART AD: Differential Survival



Ballard et al. Lancet Neurology 2009

Int J Geriatr Psychiatry. 2008 Sep;23(9):889-95. doi: 10.1002/gps.1998.

Stopping antipsychotic drug therapy in demented nursing home patients: a randomized, placebo-controlled study--the Bergen District Nursing Home Study (BEDNURS).

Ruths S[1], Straand J, Nygaard HA, Aarsland D.

LTC patients (3 months or more) age 65+ on long term antipsychotic therapy (3 months or more) taking a stable dose of haloperidol, risperidone or olanzapine for BPSD

Methods:

- N = 55; Duration: 4 weeks
- Changes in BPSD total scores, individual symptom scores and factor scores from baseline; as well as proportion improved/worsened behaviour.
- Symptom assessment was based on Neuropsychiatric Inventory (NPI) Questionnaire

Results:

- By study completion, 23/27 (intervention) patients were still off antipsychotics
- Changes in behavioral symptoms did not differ significantly as per individual symptom scores, total NPI scores, or the five principal NPI-factors *(p=0.18)*

Post Follow Up:

- Intervention group at 1 and 3 months: 11/24 (46%) and 8/24 (33%) patients remained off antipsychotics
- Control group at 1 and 3 months: 10/28 (36%) and 6/27 (22%)

Quetiapine for primary insomnia: A double blind, randomized controlled trial

Article *in* Journal of the Medical Association of Thailand = Chotmaihet thangphaet 93(6):729-34 · June 2010 *with* 205 Reads
Source: PubMed

Objective:

- Evaluate the clinical efficacy of quetiapine 25 mg for the treatment of primary insomnia

Study Design:

- Double blind, RCT

- N = 13; mean age 45.95 yrs (25-62)

- Patients with DSM-IV TR defined primary insomnia were asked to record a sleep diary one week prior to treatment, followed by 2 weeks of nightly treatment with either quetiapine 25 mg or placebo

- Primary outcomes: total sleep time (TST), sleep latency (SL), daytime alertness & functioning & sleep satisfaction
- Secondary Outcomes: safety and tolerability

Results

Table 2. Treatment results

	Placebo Mean (SD)	Quetiapine Mean (SD)	p-value
Total sleep time (minutes)			
Before treatment	289.64 (67.90)	222.55 (142.93)	
After treatment	361.88 (85.37)	347.47 (100.87)	
Differences between before and after	72.24 (45.02)	124.92 (82.90)	0.193
Sleep latency (minutes)			
Before treatment	71.16 (52.53)	162.65 (129.59)	
After treatment	47.44 (30.38)	66.50 (51.21)	
Differences between before and after	23.72 (26.76)	96.16 (85.51)	0.070
Sleep satisfaction (scored on VAS)			
Before treatment	46.17 (20.00)	41.43 (23.75)	
After treatment	58.33 (23.17)	59.29 (14.56)	
Differences between before and after	12.17 (10.01)	18.33 (19.41)	0.505

VAS = visual analogue scale

Tassniyom, Kanida et al. Journal of the Medical Association of Thailand (2010)

Insomnia: Recommendations

- For adults with primary insomnia treated for any duration or secondary insomnia in which underlying comorbidities are managed the following is recommended:
  - Stop antipsychotics if patient has been taking it for a short period of time (<6 weeks); tapering is not needed (good practice recommendation)
  - If patient has been taking the antipsychotic for a longer period of time consider tapering the dose first before stopping
- QoE for effectiveness of atypical antipsychotics for insomnia - very low
- All patients should be counseled about non-pharmacologic approaches to sleep

Bjerre L et al. Canadian Family Physician 2018

Centre for Effective Practice

Use of Antipsychotics in Behavioural and Psychological Symptoms of Dementia (BPSD) Discussion Guide

Effectivepractice.org/academicdetailing April 2016

Approach

Important principles include:

- Being resident-centred,
- Being mindful of benefits, risks and safety concerns,
- Using an interprofessional team approach and validated tools,
- Prescribing conservatively, and,
- Reassessing regularly for opportunities to deprescribe medications that are no longer needed.

As always, efforts must be made to individualize any treatment decisions for the resident, with consideration given to caregivers, family members, as well as staff.

Identify BPSD Symptom Clusters

Psychosis

Delusions
Hallucinations
Misidentification
Suspicious

Aggression

Defensive
Resistance to care
Verbal
Physical

Agitation

Dressing/undressing
Pacing
Repetitive actions
Restless/anxious

Depression

Anxious
Guilty
Hopeless
Irritable/screaming
Sad, tearful
Suicidal

Mania

Euphoria
Irritable
Pressured speech

Apathy

Amotivation
Lacking interest
Withdrawn

Assessment of Behavioral/Psychological Symptoms of Dementia

Rationale:

- Help in identifying possible contributors to symptoms
- Establish baseline level and pattern of symptoms to assess later treatment response

Common Precipitants

- Hunger, fatigue, pain, too hot, or too cold
- Recent medication change or change in adherence → increased symptoms, side effects, drug interactions
- Physical issues such as infection
- Discomfort or distress related to constipation, incontinence, and other bowel or bladder issues
- Under-stimulation or over-stimulation (e.g., due to boredom, loneliness, noise, clutter or other environmental factors)

American Psychiatric Association 2017

Common Contributors

- Vision or hearing deficits
- Confronted with cognitively challenging situations or demands
- Being assisted with or rushed to complete tasks such as bathing, dressing, or other activities of daily living
- Feeling a loss of privacy, modesty, or other loss of control
- Sensing frustration, anxiety, or other emotional distress of caregivers

American Psychiatric Association 2017

Clinical Frailty Scale

1. **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2. **Well** – People who have no active disease symptoms but are less fit than Category1. Often, they exercise or are very active occasionally, e.g. seasonally.

3. **Managing Well** – People whose medical problems are well controlled, but are not regularly active beyond routine walking.

4. **Vulnerable** – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up," and / or being tired during the day.

5. **Mildly Frail** – These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6. **Moderately Frail** – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.

7. **Severely Frail** – Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8. **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** – Approaching the end of life. This category applies to people with a life expectancy < 6 months, who are not otherwise evidently frail.

Where dementia is present, the degree of frailty usually corresponds to the degree of dementia:

- **Mild dementia** – includes forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.
- **Moderate dementia** – recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.
- **Severe dementia** – they cannot do personal care without help.

K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–495

Geriatric Medicine Research, Dalhousie University, Halifax, Canada

Non-pharmacological Approaches

- Reduce environmental clutter and noise
- Remove items that could be thrown or that upset patient
- Optimize lighting and give cues to heighten orientation
- Provide eyeglasses, hearing aids, mobility support, etc.
- Consider approaches based on patient history/preferences: hand massage, pet therapy, music listening
- Caregiver education: reflective practice, skills targeting behavioral challenges, and enhancing coping techniques

American Psychiatric Association 2017

Environment Considerations

- Eliminate misleading stimuli
    - Clutter, TV, radio, noise, people, reflections in mirrors/dark windows, pictures/décor
- Reduce environmental stress
    - Caffeine, extra people, holiday decorations, public TV
- Adjust stimulation
    - If over-stimulated, reduce noise, activity, confusion
    - If under-stimulated, increase activity/involvement
- Enhance function
    - Increase lighting, to reduce misinterpretation
    - Add signs, cues, or pictures to promote way-finding
- Adapt the physical setting according to individual preference
    - Secure outdoor areas
    - Home-like features
    - Smaller, segmented recreational and dining areas
    - Spa-like bathing facilities

American Psychiatric Association (APA)

- APA recommends that nonemergency antipsychotic medication should only be used for the treatment of agitation or psychosis in patients with dementia when symptoms are severe, dangerous, and/or cause significant distress to the patient. (1B)
- Expert consensus suggests that antipsychotics can be used appropriately in patients with dementia in the context of dangerous agitation or psychosis to:
  - improve patient's quality of life
  - reduce patient distress
  - reduce the risk of violence
  - decrease caregiver burden
- Randomized placebo-controlled trials suggest some efficacy for risperidone in treating psychosis and for risperidone, olanzapine, and aripiprazole in agitation

American Psychiatric Association 2017

Considerations in Medication Selection

Factors that experts noted may influence their prescribing in individuals with dementia:

- Aripiprazole: Long half-life, potential for drug-drug interactions, partial agonist mechanism of action, greater rates of akathisia
- Olanzapine: Greater likelihood of anticholinergic effects, sedation, metabolic effects, and weight gain
- Risperidone: Greater likelihood of extrapyramidal symptoms and hyperprolactinemia
- Ziprasidone: Changes in absorption with food and greater likelihood of QTc prolongation

American Psychiatric Association 2017

Comparison of Antipsychotics

	Drug Generic (Brand)	Efficacy or evidence in BPSD therapy	↑ BP[32]	Ach	Sedation	EPS	TD[33]	Diabetes	Weight Gain[27]	Usual Dose	$/Month
Atypicals	Risperidone* (Risperdal)[25, 26, 34]	• Indicated for severe dementia of the Alzheimer type (Health Canada) • Evidence for efficacy in agitation, aggression & psychosis	++	++	++	++	+	++	↑↑↑ (0.7lb/ month)	0.125mg – 2.0mg/d QHS (or divided BID)	$10-27
	Olanzapine* (Zyprexa)[25, 26, 34]	• Off-label use in BPSD • Evidence for efficacy in agitation & aggression	+	+++	+++	++	+	+++	↑↑↑ (1.0lb/ month)	1.25mg – 7.5mg/d	$17-38
	Aripiprazole* (Abilify)[34]	• Off-label use in agitation or aggression[18] • Evidence for efficacy in agitation & aggression • Not eligible for dementia or BPSD in the elderly (ODB criteria, Therapeutic Note) • Not for psychosis (same as placebo)	+	+	++	+	+	–	↑	2.0mg – 12.5mg QHS	$112-260
	Quetiapine (Seroquel)[25, 26, 34]	• Off-label use in BPSD • Lacks evidence for efficacy in BPSD agitation, aggression & psychosis • Consider in Lewy Body dementia, Parkinson's (low EPS) • Note: although used, not indicated, and lacking evidence for insomnia	++	+++	+++	+	+	+++	↑↑ (0.4lb/ month)	12.5mg – 200mg/d (divided QHS-TID)	$10-59
Typicals	Haloperidol (Haldol)	• Useful short term in acute BPSD or delirium	+	+	+	+++	+++	++	↑↑	0.25mg – 2.0mg/d	$14-25
	Loxapine (Loxapac, Xylac)[2]	• Consider if other agents have failed and severe, persistent, dangerous behaviour continues • Severe, acute BPSD • Not to be used long-term due to adverse effects	++	++	+++	+++	+++	+	–	5.0mg – 10mg BID	$18-27

Additional QTc Data for Antipsychotics

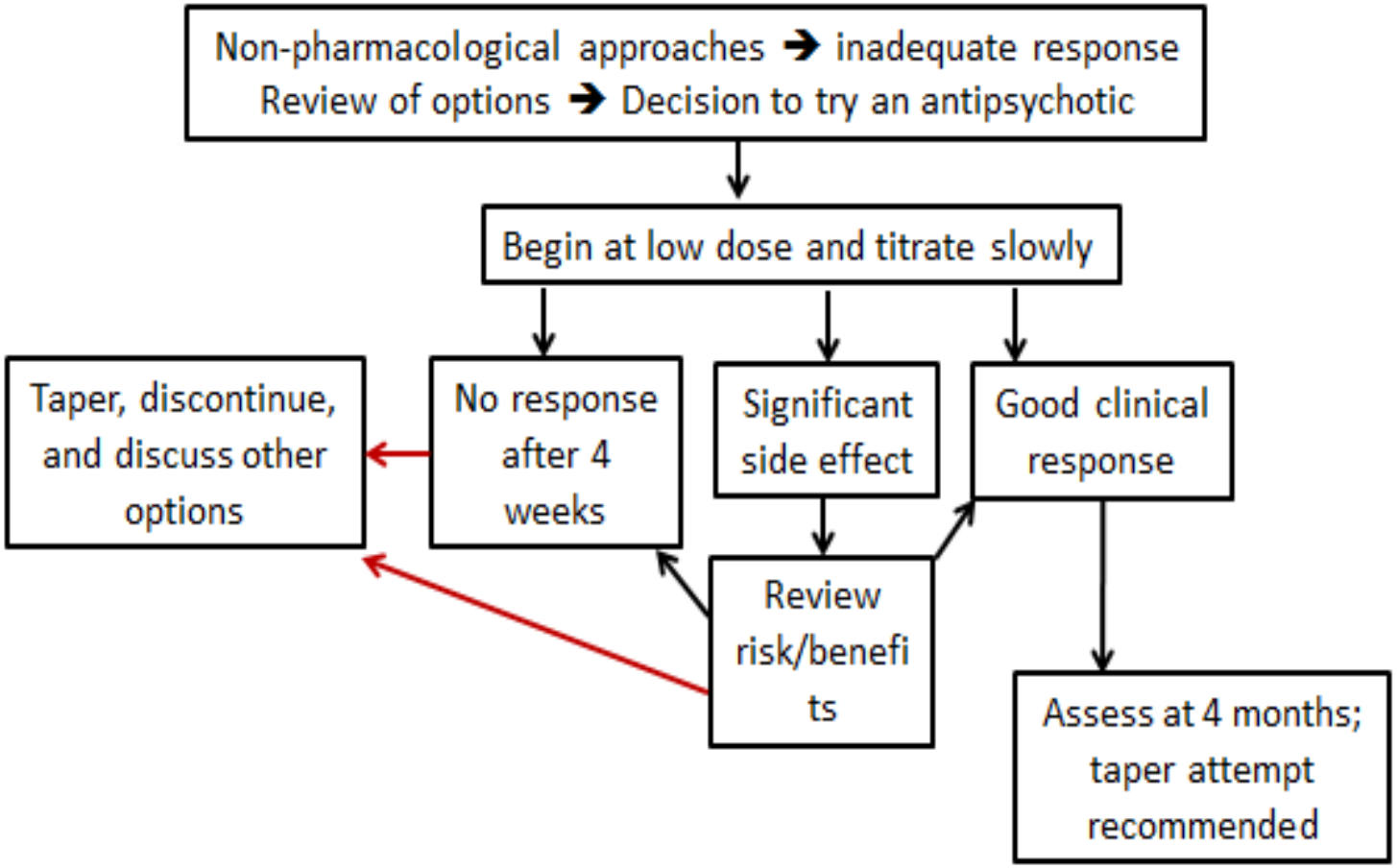
Effects of orally-administered antipsychotics on the QT interval

Drug	Mean increase in QTc (ms)	% of subjects with > 60 ms increase in QTc
Thioridazine	35.8	29
Ziprasidone	20.6	21
Quetiapine	14.5	11
Risperidone	10.0	4
Olanzapine	6.4	4
Haloperidol	4.7	4

Data adapted from the U.S. Food and Drug Administration's Center for Drug Evaluation and Research, Psychopharmacological Drugs Advisory Committee

OVERVIEW: ANTIPSYCHOTIC USE

AMERICAN PSYCHIATRIC ASSOCIATION



Suggested Tapering Strategies

For those prescribed antipsychotics for the treatment of BPSD:

- Reduce to 75%, 50%, and 25% of the original dose on a biweekly basis before stopping

  OR

- Reduce previous dose by approx. 50% every week down to 25% of the initial dose, then stop

Note: *For patients with severe baseline BPSD symptoms slower tapering is recommended*

- Close monitoring for withdrawal symptoms, and establishing a clear intervention plan emphasizing the use of non-pharmacologic approaches first, in the event of increased severity or recurrence of neuropsychiatric symptoms

- Furthermore, tapering might need to be individualized depending on the starting dose, available dosage forms, and how tapering is tolerated

Bjerre L et al. Canadian Family Physician 2018

Take Home Message

- Overuse of medication is acknowledged to be a key contributor to polypharmacy, with negative effects on health
- Antipsychotics have modest efficacy in the short term treatment of BPSD in AD, but should only be used as a last resort & should not be used for long term treatment
- Review identified that antipsychotics can be safely deprescribed in many patients with BPSD
- Limited evidence supporting the use of antipsychotics for treating insomnia
- When deprescribing antipsychotics, patient, family member & caregiver involvement is crucial

QUESTIONS?

References

- American Psychiatric Association Guidelines On The Use Of Antipsychotic To Treat Agitation or Psychosis In Patients with Dementia. https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890426807
- Centre for Effective Practice. Use of Antipsychotics in Behavioural and Psychological Symptoms of Dementia (BPSD) Discussion Guide. [Internet]. C2015. Long-term Care (LTC) 2nd Edition; 2016 April; [cite 2019 Oct 10]; Available from: https://cep.health/media/uploaded/UseofAntipsychotics_LTC2016-2.pdf
- Bjerre L Et al. Deprescribing antipsychotics for behavioural and psychological symptoms of dementia and insomnia. Evidence-based clinical practice guideline. Canadian Family Physician January 2018, 64 (1) 17-27
- https://www.choosingwisely.org/clinician-lists/
- Stopping antipsychotic drug therapy in demented nursing home patients: a randomized, placebo-controlled study—The Bergen District Nursing Home Study (BEDNURS)
- Tassniyom, Kanida et al. “Quetiapine for primary insomnia: a double blind, randomized controlled trial.” Journal of the Medical Association of Thailand = Chotmaihet thangphaet 93 6 (2010): 729-34.
- Ballard C et al. The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial. Lancet Neurol 2009; 8: 151–57 Published Online January 9, 2009