Pharmacological Management Of Neuropsychiatric Symptoms Of Dementia: Best Practice And New Evidence

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brainXchange

FACULTY/PRESENTER DISCLOSURE

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DISCLOSURE OF COMMERCIAL SUPPORT

- This program has received no in-kind support from outside organizations

KEY OBJECTIVES

By the end of the presentation, the participant is expected to be able to:

- 1.) Understand factors that contribute to the development of neuropsychiatric symptoms (NPS);
- 2.) Review recent evidence in pharmacological management of neuropsychiatric symptoms;
- 3.) Apply this knowledge in clinical settings.

NEUROPSYCHIATRIC SYMPTOMS

- Non-cognitive symptoms associated with dementia
- Also known as Behavioral and Psychological Symptoms of Dementia (BPSD)
  - International Psychogeriatrics Association 1996 “Signs and symptoms of disturbed perception, thought content, mood, or behavior that frequently occur in patients with dementia”[1]

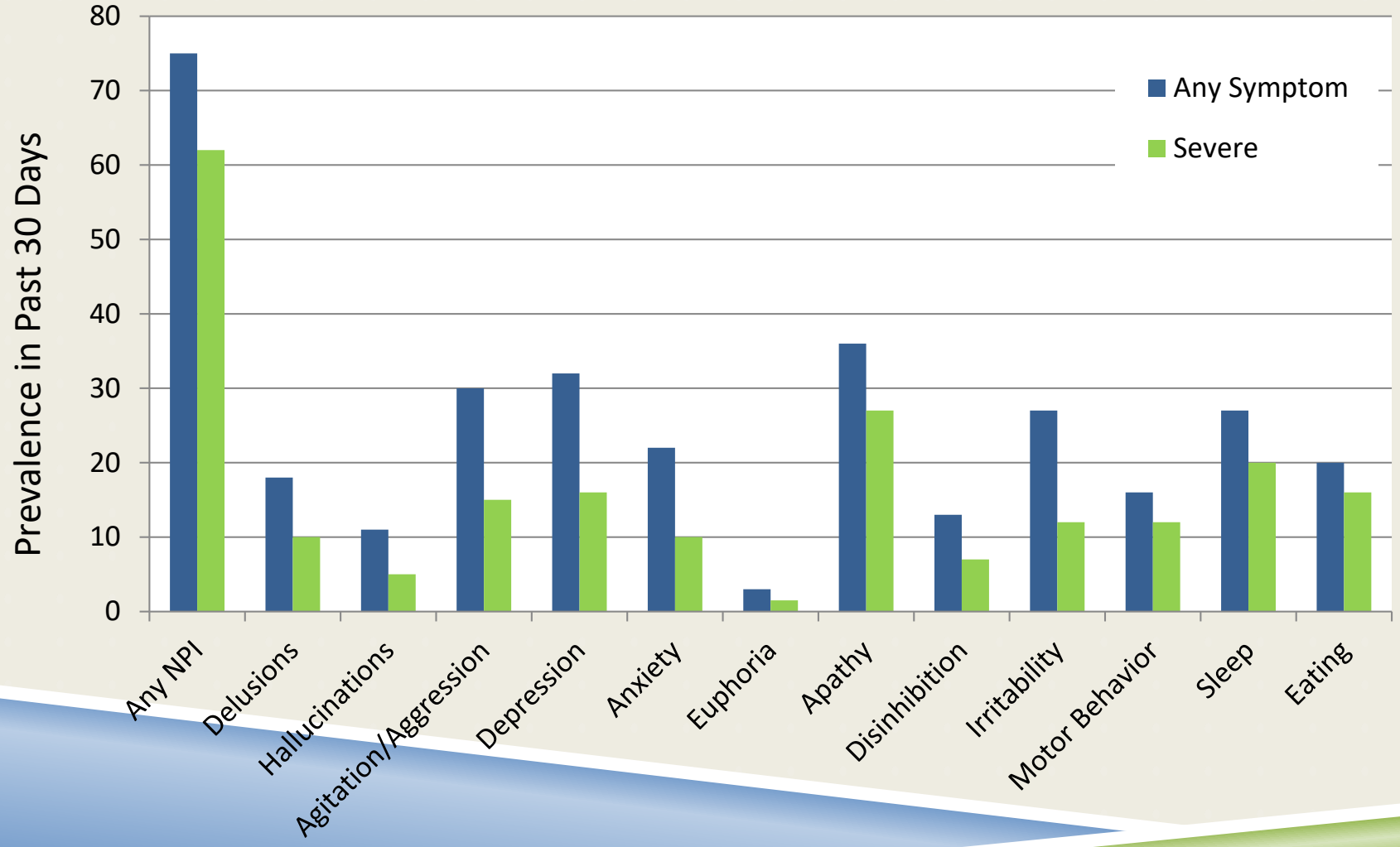
1. Finkel, Int Psychogeriatr, 1996; 8(suppl 3):497-500

ALZHEIMER'S ASSOCIATION CLASSIFICATION

- Agitation
  - "inappropriate verbal, vocal, or motor activity that is not an obvious expression of need or confusion"[1]
- Psychosis
  - Delusions, hallucinations
- Depression
- Apathy
  - "absence of responsiveness to stimuli as demonstrated by a lack of self-initiated action"
- Sleep

1. Cohen-Mansfield, J Gerontol, 1989

PREVALENCE OF NPS IN ALZHEIMER'S DISEASE



Lyketsos, JAMA, 2002

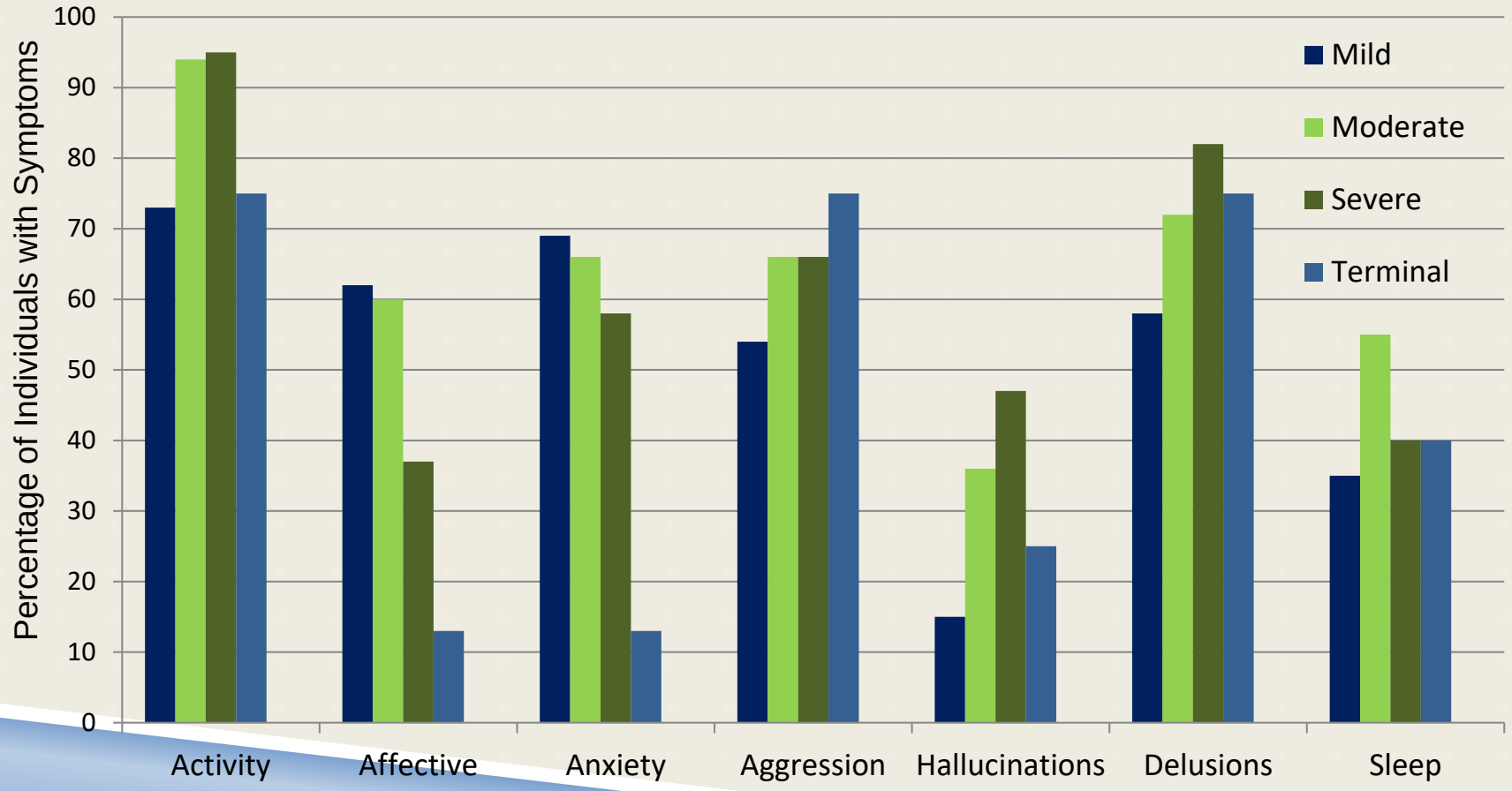
PREVALENCE OF NPS IN LONG-TERM CARE

- 60% of individuals LTC settings have dementia[1]
- Overall prevalence of NPS:
  - Median prevalence of any NPS: 78%

- Prevalence of NPS[2]:
  - Psychosis 15 – 30%
  - Depression: 30 – 50%
  - Physical agitation: 30%
  - Aggression: 10 – 20%

1. Seitz, *Int Psychogeriatr,* 2010
2. Zuidema, J Geriatr Psych Neurol, 2007

ASSOCIATIONS WITH STAGE OF ILLNESS



Chen, Am J Geriatr Psychiatry, 2000

PERSISTENCE OF NPS

- Neuropsychiatric symptoms are often chronic[1,2]
  - More likely to persist: delusions, depression, aberrant motor behavior
  - Less likely to persist: hallucinations, disinhibition

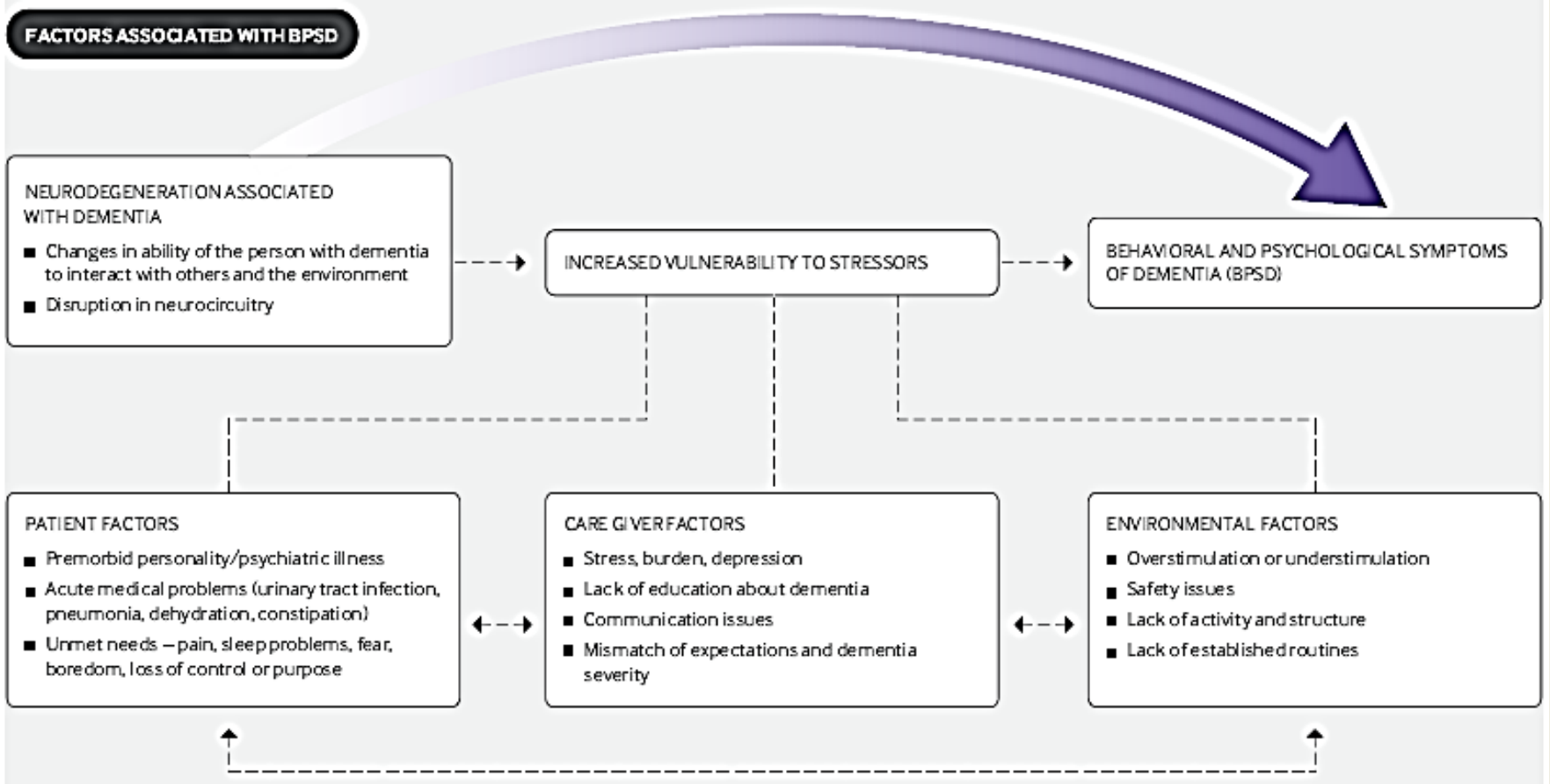
1. Steinberg, Int J Geriatr Psychiatry, 2004
2. Aalten, Int J Geriatr Psychiatry, 2005

ASSOCIATIONS WITH PROGRESSION AND MORTALITY

	Severe Dementia (Hazard Ratio)	P value	Mortality (Hazard Ratio)	P value
Psychosis	2.00	0.03	1.54	0.01
Affective	1.51	0.1	1.51	0.003
Agitation/ Aggression	2.95	0.04	1.94	0.004
Apathy	1.55	0.17	1.26	0.21
Any significant NPS	2.68	0.001	1.95	<0.001

Peters, Am J Psych, 2015

UNDERSTANDING NPS



Kales, BMJ, 2015

DICE APPROACH

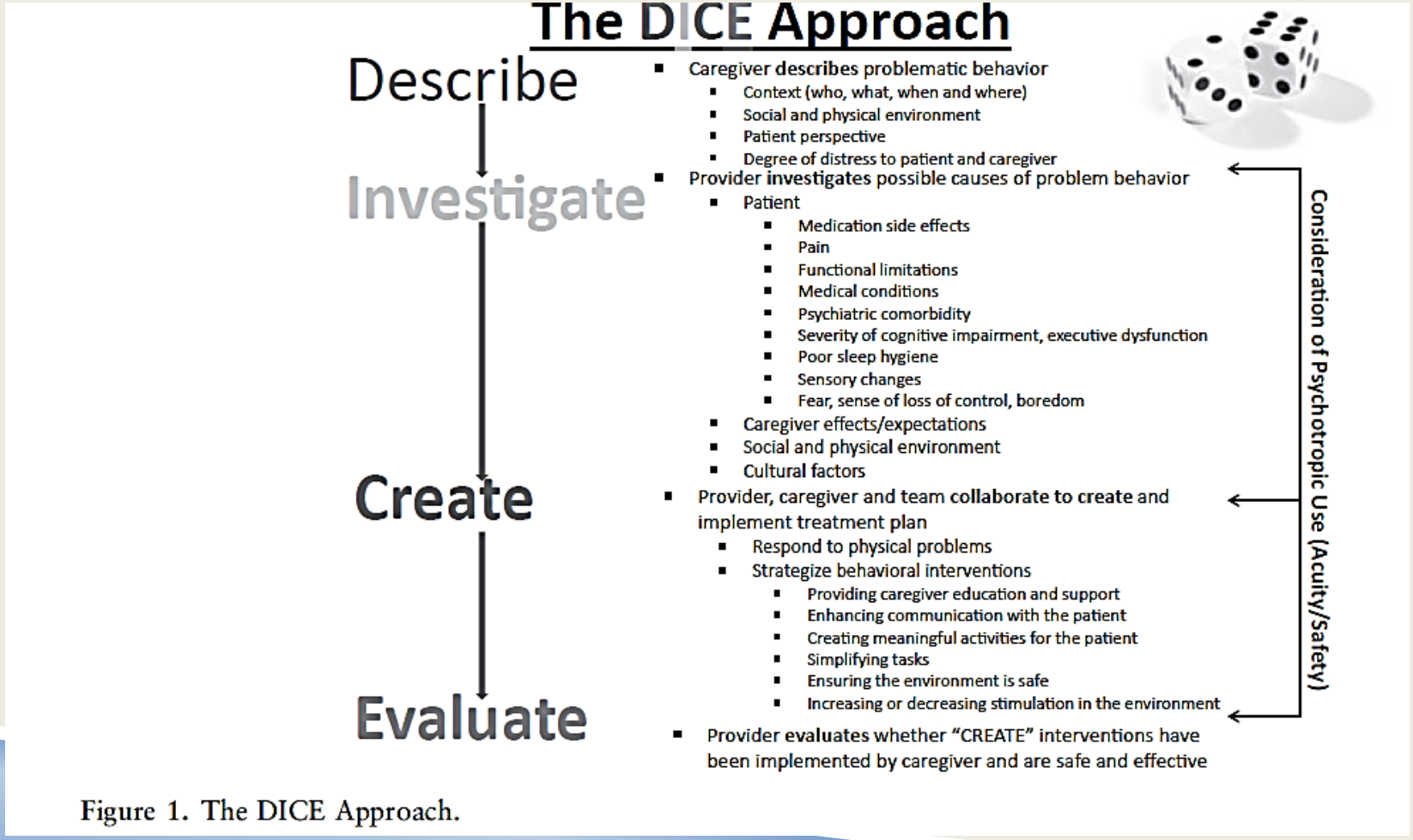
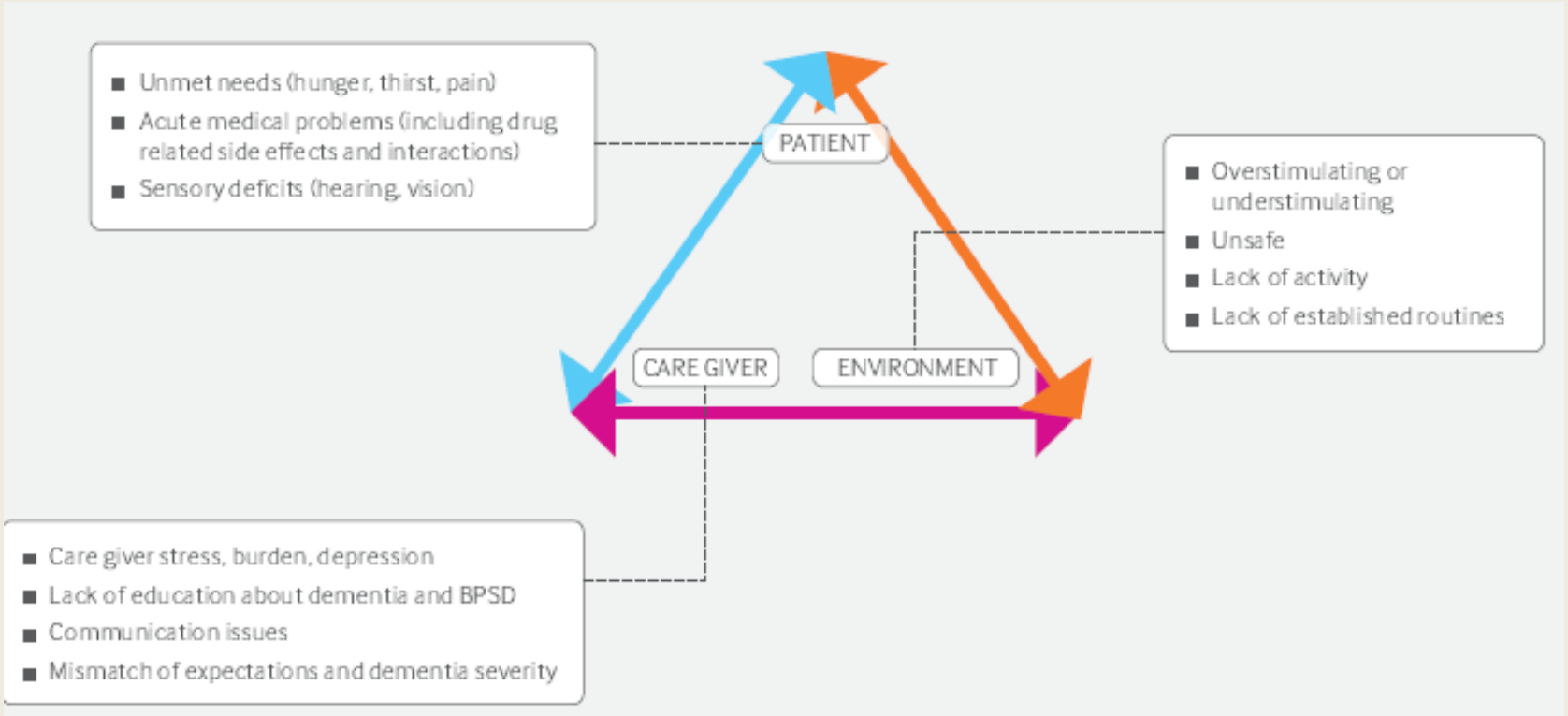


Figure 1. The DICE Approach.

Kales, JAGS, 2014

DICE APPROACH



Kales, BMJ, 2015

PAIN IN DEMENTIA

- Pain is common and undertreated in older adults
  - 50 – 80% of individuals in LTC have pain[1]
- Assessment of pain in individuals with advanced dementia particularly challenging
  - Pain can present as agitation
  - Language and communication difficulties
  - Recall of pain and changes over time

1. Fox, CMAJ, 1999

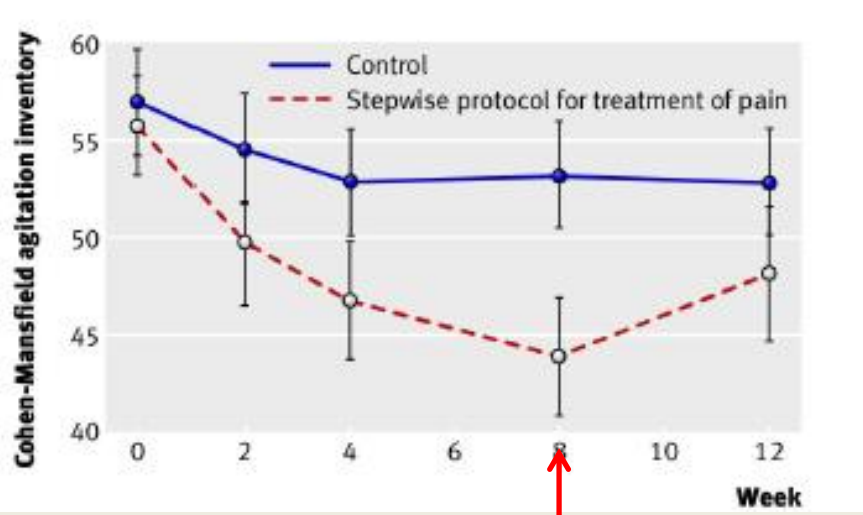
PAIN TREATMENT PROTOCOL

Step	Pain Treatment at Baseline	Study Treatment	Dosage	Number (%) of residents (N=175)
1	No analgesia, or low dose acetaminophen	Acetaminophen	Max 3g/day TID	120 (69)
2	Full dose acetaminophen or low-dose morphine	Morphine	5 mg BID, max 10 BID	4 (2)
3	Low-dose buprenorphine or unable to swallow	Buprenorphine patch	5 mcg/h, max 10 mcg/h	39 (22)
4	Neuropathic pain	Pregabalin	25 mg OD, max 300 OD	12 (7)

1. Husebo, BMJ, 2011

PAIN TREATMENT PROTOCOL

CMAI Total Score



Medications Withdrawn

- Benefits also noted on overall NPS, and pain
- No effect on cognition or ADL functioning
- 9/175 (5%) treatment group withdrew d/t AE

1. Husebo, BMJ, 2011

GENERAL PRINCIPLES TO MANAGING NPS

- Non-pharmacological treatments should be used first whenever available
- Even when NPS are caused by specific etiologies (pain, depression, psychosis) non-pharmacological interventions should be utilized with medications
- All non-pharmacological interventions work best when tailored to individual needs and background
- Family and caregivers are key collaborators and need to involved in treatment planning

NONPHARMACOLOGICAL INTERVENTIONS

- Training caregivers or
- Mental health consultations
- Participation in pleasant events
- Exercise
- Music
- Sensory stimulation (e.g. touch, Snoezelen, aromatherapy)

Cohen-Mansfield, Am J Geriatr Psychiatry, 2001
Livingston, Am J Psychiatry, 2005
Seitz, JAMDA, 2012

PHARMACOLOGICAL MANAGEMENT OF NPS

- Medications should be used for severe NPS or patient safety, in conjunction with non-pharmacological approaches
- Prescribing requires assessment of capacity and informed consent
- Dosages are lower than that used in younger populations and need to be adjusted cautiously
- Elderly with dementia are more susceptible to some side-effects such as sedation, cognitive decline, EPS

NPS THAT MAY RESPOND TO MEDICATIONS

- Aggression*
- Agitation*
- Psychosis*
- Depression
- Anxiety
- Apathy
- Sleep

MEDICATIONS FOR AGITATION/AGGRESSION AND PSYCHOSIS

- Atypical antipsychotics
- Typical antipsychotics (conventional)
- Antidepressants
  - SSRIs
  - Trazodone
- Other medications
  - Cannabinoids
  - Dextromethorphan/Quinidine
- Cognitive Enhancers

ATYPICAL ANTIPSYCHOTICS

- *Risperidone, aripiprazole*, and olanzapine have the strongest evidence to treat psychosis and agitation in dementia[1,2]
- Number needed to treat for significant improvement: 5 – 14
- Odds ratio for significant improvement compared to placebo: 1.5 – 2.5

1. Schneider, Am J Geriatr Psychiatry, 2006
2. Ballard, Coch Database Syst Rev, 2008
3. Fontaine, *J Clin Psych,* 2003
4. Tariot, Am J Geriatr Psychiatry, 2006
5. Verhey, Dementia Geriatr Cogn Disord, 2006

ANTIPSYCHOTICS FOR DEMENTIA: CATIE-AD

- Large RCT (N=421) of outpatients with Alzheimer's comparing risperidone, olanzapine, quetiapine and placebo for psychosis, agitation or aggression over 36 weeks
- Outcomes:
  - Time to discontinuation due to any cause
  - Global impression
  - Adverse events

1. Schneider, *New Eng J Med*, 2006

CATIE-AD

- No difference in groups on time to discontinuation due to any cause
- Olanzapine and risperidone > placebo and quetiapine on discontinuations due to lack of efficacy
  - Overall discontinuation rate of 63% by 12 weeks
- Discontinuations due to adverse events favored placebo
- No difference in rates of global clinical improvement

1. Schneider, *New Eng J Med*, 2006

NPS THAT RESPOND TO ANTIPSYCHOTICS

- Olanzapine and risperidone associated with overall improvement in NPS[1]
  - Hostility, psychosis, agitation most likely to improve

1. Sultzer, *Am J Psychiatry*, 2008

ATYPICAL ANTIPSYCHOTICS DOSING

	Initial Dose	Titration Schedule	Maximum dosage
Risperidone	0.5 mg total (given OD or BID)	0.25 - 0.5 mg every 3 – 7 days	2 mg
Olanzapine	2.5 – 5.0 mg OD	2.5 – 5.0 mg every 3 – 7 days	10 mg
Aripiprazole	2 – 5 mg	2 – 5 mg every 3 – 7 days	10 mg
Quetiapine	12.5 mg BID	25 mg in divided doses every 3 – 7 days	200 mg

Consider switching antipsychotics if no benefit or limited benefit observed after 2 weeks of therapeutic dose

SERIOUS ADVERSE EVENTS

- Mortality: OR=1.6, absolute risk ~1%[1,2]
  - Number needed to harm: 100
  - Infections, cardiovascular events
- Stroke: RR=2.7, absolute risk~1%[2,3]
- Any serious adverse events within 30 days[4]
  - Atypical: 13.9% (OR: 3.5, 3.1 – 4.1)
  - Typical: 16% (OR=4.2, 95% CI: 3.7 – 4.8)
  - No antipsychotic: 4.4%

1. Schneider, JAMA, 2005
2. Schneider, Am J Geriatr Psychiatry, 2006
3. Herrmann, CNS Drugs, 2005
4. Rochon, *Arch Intern Med*, 2008

COMPARATIVE SAFETY OF ANTIPSYCHOTICS

Table 2. Crude Death Rates During a 180-Day Observation Period Among Patients With Dementia Starting Therapy With a New Medication

Medication	No. of Pair[a]	Death, No. (%)		Risk Difference, % (95% CI)[b]	NNH (95% CI)[b]
		Users	Nonusers		
Haloperidol	1921	398 (20.7)	162 (8.4)	3.8 (1.0 to 6.6)[c]	26 (15 to 99)
Olanzapine	1908	265 (13.9)	187 (9.8)	2.5 (0.3 to 4.7)[d]	40 (21 to 312)
Quetiapine	4621	545 (11.8)	378 (8.2)	2.0 (0.7 to 3.3)[c]	50 (30 to 150)
Risperidone	6338	883 (13.9)	538 (8.5)	3.7 (2.2 to 5.3)[c]	27 (19 to 46)
Valproic acid	901	110 (12.2)	65 (7.2)	4.1 (−1.0 to 9.2)	NA[e]
Antidepressant	29 704	2472 (8.3)	2367 (8.0)	0.6 (0.3 to 0.9)[c]	166 (107 to 362)

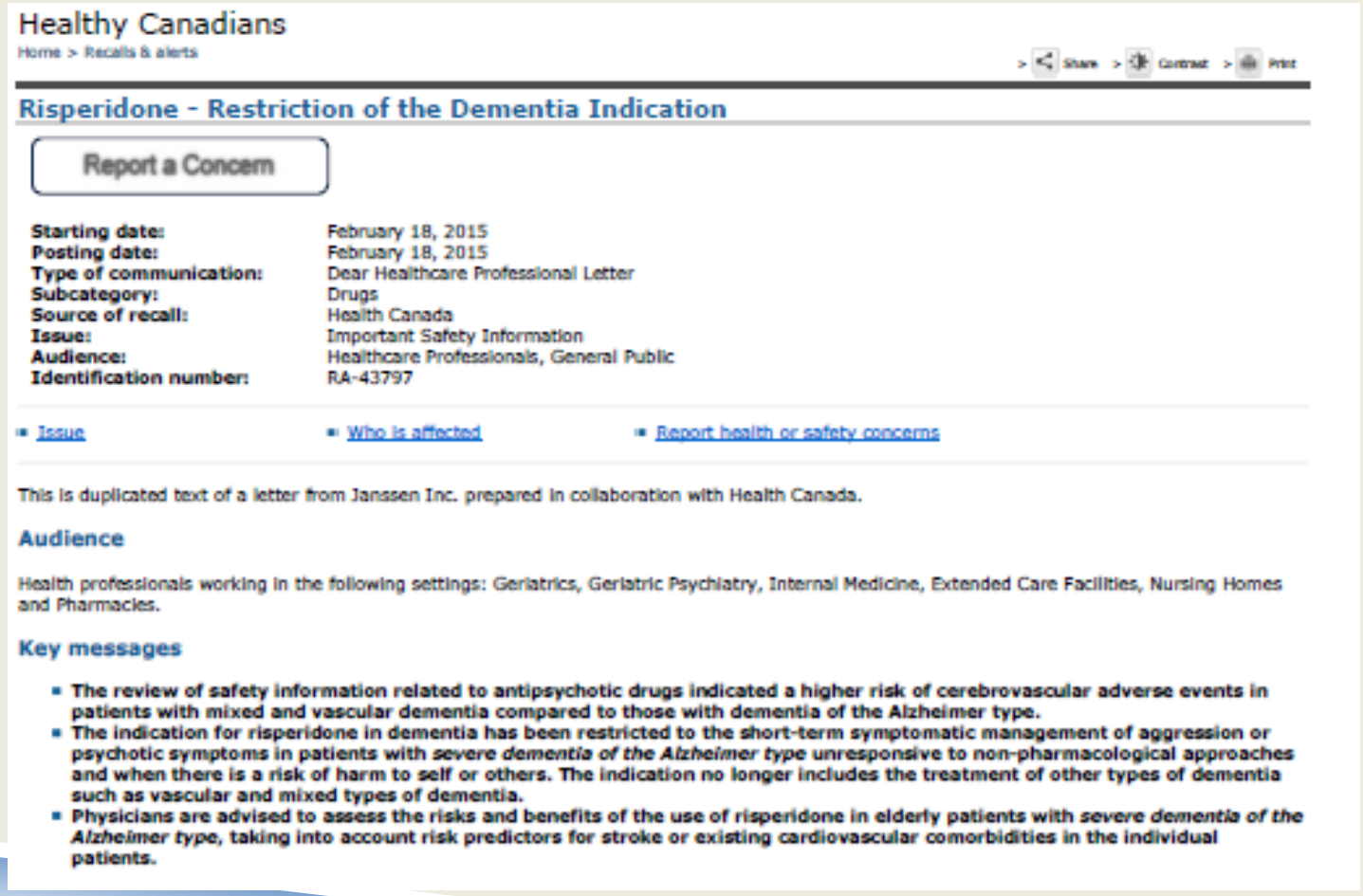
1. Kales, JAMA Psychiatry, 2015

COMMON ADVERSE EVENTS

- Somnolence: OR=2.8, absolute risk~10%[1]
- Gait changes: OR=3.2, AR=10%[1]
- Falls and fractures: OR = 1.5 – 2.0
- Extrapyramidal symptoms[1]
  - Risperidone
- Weight gain, dyslipidemia[2,3]
  - Greatest risk with olanzapine and quetiapine, women at highest risk

1. Schneider, Am J Geriatr Psychiatry, 2006
2. Schneider, N Eng J Med, 2006
3. Zheng, Am J Psychiatry, 2009

UPDATED RISPERIDONE INDICATION



Healthy Canadians

Home > Recalls & alerts

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Risperidone - Restriction of the Dementia Indication

Report a Concern

Starting date:	February 18, 2015
Posting date:	February 18, 2015
Type of communication:	Dear Healthcare Professional Letter
Subcategory:	Drugs
Source of recall:	Health Canada
Issue:	Important Safety Information
Audience:	Healthcare Professionals, General Public
Identification number:	RA-43797

- Issue
- Who is affected
- Report health or safety concerns

This is duplicated text of a letter from Janssen Inc. prepared in collaboration with Health Canada.

Audience

Health professionals working in the following settings: Geriatrics, Geriatric Psychiatry, Internal Medicine, Extended Care Facilities, Nursing Homes and Pharmacies.

Key messages

- **The review of safety information related to antipsychotic drugs indicated a higher risk of cerebrovascular adverse events in patients with mixed and vascular dementia compared to those with dementia of the Alzheimer type.**
- **The indication for risperidone in dementia has been restricted to the short-term symptomatic management of aggression or psychotic symptoms in patients with *severe dementia of the Alzheimer type* unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others. The indication no longer includes the treatment of other types of dementia such as vascular and mixed types of dementia.**
- **Physicians are advised to assess the risks and benefits of the use of risperidone in elderly patients with *severe dementia of the Alzheimer type*, taking into account risk predictors for stroke or existing cardiovascular comorbidities in the individual patients.**

1. Health Canada, February, 2015

COGNITIVE EFFECTS OF ANTIPSYCHOTICS

- Atypical antipsychotics associated with a MMSE score -2.4 over 36 weeks compared to placebo[1]
  - Equivalent to approximately 1 year additional decline
- MMSE -1 point over 8 – 12 week trials[2]
  - Often LTC population with low MMSE at baseline

1. Vigen, *Am J Psychiatry*, 2011
2. Schneider, *Am J Geriatr Psychiatry*, 2006

TYPICAL ANTIPSYCHOTICS

- Effective in reducing symptoms of aggression, agitation and psychosis[1-3]
- Adverse event rates higher with typicals when compared to atypicals
- Risk of stroke[4,5] and death[6,7] similar to atypical antipsychotics

1. Schneider, J Am Geriatr Soc, 1990
2. Lanctot, J Clin Psychiatry, 1988
3. Lonergan, Cochrane Data Syst Rev, 2002
4. Gill, BMJ, 2005
5. Herrmann, Am J Psychiatry, 2004
6. Wang, N Eng J Med, 2005
7. Gill, Ann Intern Med, 2007

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

- SSRIs have some benefits in treating agitation, psychosis and other NPS[1] (N=7)
- Citalopram more effective than placebo in reducing NPS[2]
  - Doses of 20 – 30 mg daily (Note: FDA warning about citalopram doses above 20 mg daily)
- Sertraline had modest effect on agitation compared to placebo[3]
  - Doses 25 – 100 mg daily

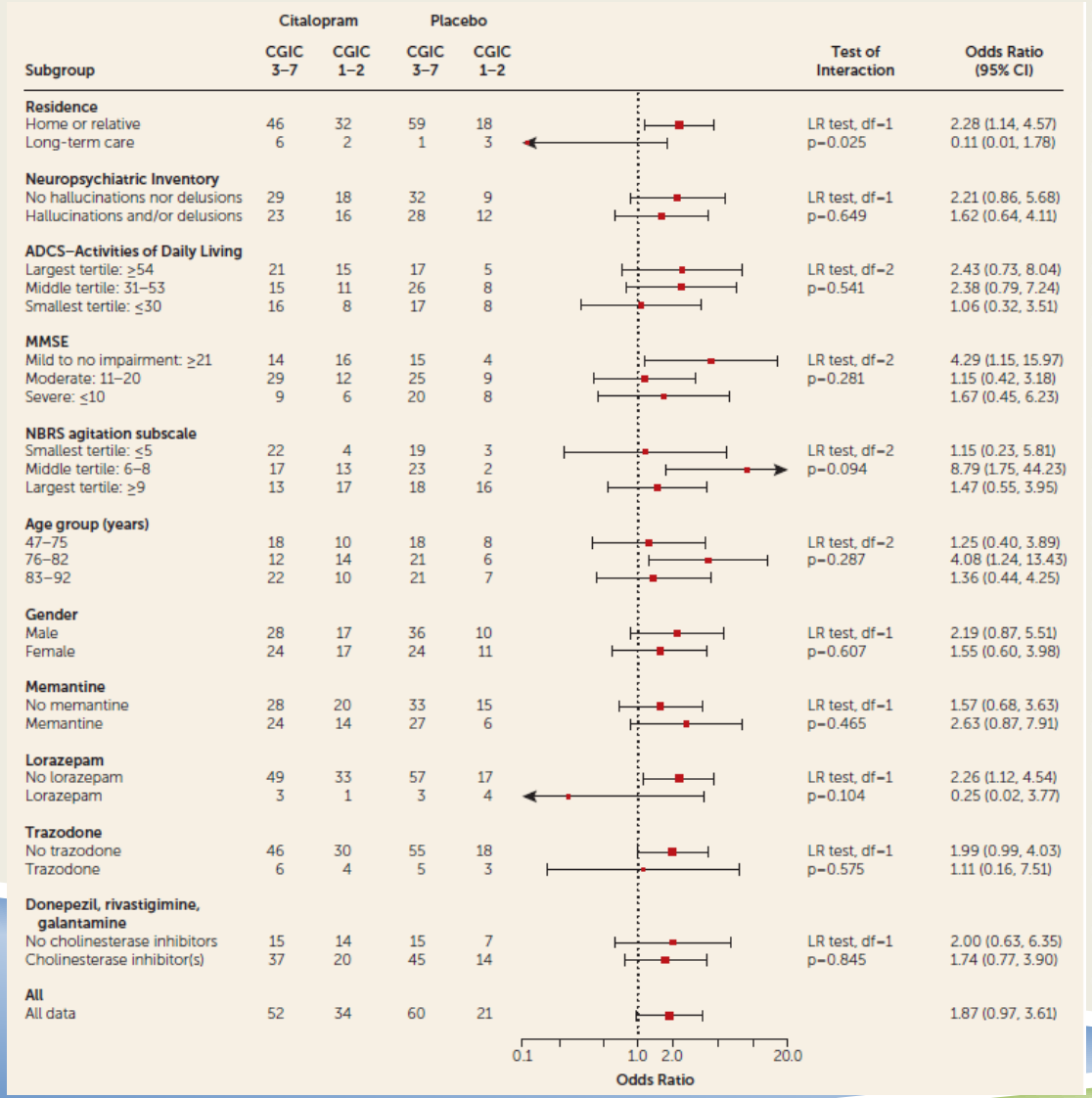
1. Seitz, Cochrane Data Syst Rev, 2011
2. Pollock, Am J Psychiatry, 2002
3. Finkel, Int J Geriatr Psychiatry, 2004

CITALOPRAM FOR AGITATION: CITAD

- RCT of citalopram (10 – 30 mg daily) or placebo for AD patient with significant agitation
  - Majority received 30 mg of citalopram*
- Significant improvements on NBRS-A, CMAI with citalopram compared to placebo
- 40% of citalopram vs 26% of individuals with placebo had moderate or marked improvement
- Worsening of cognition noted with citalopram

Porsteinsson, JAMA, 2014

PREDICTORS OF RESPONSE TO CITALOPRAM



Subgroup	Citalopram CGIC 3–7	Citalopram CGIC 1–2	Placebo CGIC 3–7	Placebo CGIC 1–2	Test of Interaction	Odds Ratio (95% CI)
Residence						
Home or relative	46	32	59	18	LR test, df=1	2.28 (1.14, 4.57)
Long-term care	6	2	1	3	p=0.025	0.11 (0.01, 1.78)
Neuropsychiatric Inventory						
No hallucinations nor delusions	29	18	32	9	LR test, df=1	2.21 (0.86, 5.68)
Hallucinations and/or delusions	23	16	28	12	p=0.649	1.62 (0.64, 4.11)
ADCS–Activities of Daily Living						
Largest tertile: ≥54	21	15	17	5	LR test, df=2	2.43 (0.73, 8.04)
Middle tertile: 31–53	15	11	26	8	p=0.541	2.38 (0.79, 7.24)
Smallest tertile: ≤30	16	8	17	8		1.06 (0.32, 3.51)
MMSE						
Mild to no impairment: ≥21	14	16	15	4	LR test, df=2	4.29 (1.15, 15.97)
Moderate: 11–20	29	12	25	9	p=0.281	1.15 (0.42, 3.18)
Severe: ≤10	9	6	20	8		1.67 (0.45, 6.23)
NBRS agitation subscale						
Smallest tertile: ≤5	22	4	19	3	LR test, df=2	1.15 (0.23, 5.81)
Middle tertile: 6–8	17	13	23	2	p=0.094	8.79 (1.75, 44.23)
Largest tertile: ≥9	13	17	18	16		1.47 (0.55, 3.95)
Age group (years)						
47–75	18	10	18	8	LR test, df=2	1.25 (0.40, 3.89)
76–82	12	14	21	6	p=0.287	4.08 (1.24, 13.43)
83–92	22	10	21	7		1.36 (0.44, 4.25)
Gender						
Male	28	17	36	10	LR test, df=1	2.19 (0.87, 5.51)
Female	24	17	24	11	p=0.607	1.55 (0.60, 3.98)
Memantine						
No memantine	28	20	33	15	LR test, df=1	1.57 (0.68, 3.63)
Memantine	24	14	27	6	p=0.465	2.63 (0.87, 7.91)
Lorazepam						
No lorazepam	49	33	57	17	LR test, df=1	2.26 (1.12, 4.54)
Lorazepam	3	1	3	4	p=0.104	0.25 (0.02, 3.77)
Trazodone						
No trazodone	46	30	55	18	LR test, df=1	1.99 (0.99, 4.03)
Trazodone	6	4	5	3	p=0.575	1.11 (0.16, 7.51)
Donepezil, rivastigimine, galantamine						
No cholinesterase inhibitors	15	14	15	7	LR test, df=1	2.00 (0.63, 6.35)
Cholinesterase inhibitor(s)	37	20	45	14	p=0.845	1.74 (0.77, 3.90)
All						
All data	52	34	60	21		1.87 (0.97, 3.61)

Predictors of Response

Community-dwelling (vs. LTC)

MMSE > 21 (vs. lower)

Moderate symptoms (vs. Severe)

Schneider, Am J Psychiatry, 2016

QTC CHANGES IN CITAD

	Citalopram (N=24)	Placebo (N=24)	P value
Mean (SD) QTc at Week 3	432 (24)	414 (25)	
Mean (SD) Change QTc Week 3 - Baseline	14.9 (19)	-2.9 (22)	
Difference in QTc Change Citalopram - Placebo	18.1 (95% CI: 6.1 – 30.1)		0.004
N (%) > 30 ms change in QTc	7 (32)	1 (5%)	0.046
N (%) QTc prolongation*	3 (13%)	1 (4%)	0.61

*>450 msec males, > 470 msec females

Drye, PLoS One, 2014

WHICH SYMPTOMS IMPROVE WITH CITALOPRAM?

- Individuals treated with citalopram less likely to report delusions (OR: 0.4), anxiety (OR: 0.4), irritability (OR: 0.4), and had reductions in symptoms of hallucinations
- Worsening of sleep problems was greater with citalopram compared to placebo

Leonpacher, Am J Psychiatry, 2016

CITALOPRAM OR ESCITALOPRAM?

- S-entantiomer of Citalopram (Escitalopram) was associated with improvement in NPS, R-entantiomer associated with adverse effects
  - Escitalopram (Cipralex) 5 to10 mg may be a better choice than Citalopram (Celexa)

Ho, Br J Pharmaco, 2016

TRAZODONE

- 2 small RCTs of trazodone for NPS found no significant difference between trazodone and either placebo[1] or haloperidol[1-3]
  - Trazodone treated individuals had **numerically worse outcomes** when compared to placebo (+5 points worsening on the CMAI)

1. Teri, Neurology, 2000
2. Sultzer, Am J Geriatr Psychiatry, 1997
3. Seitz, Cochrane Data Syst Rev, 2011

CANNABINOIDS TO TREAT AGITATION IN DEMENTIA

- Oral THC (tetrahydrocannabinol) 4.5 mg daily was not effective in reducing agitation or other NPS
  - Outcomes were numerically worse for THC
- Small studies showing possible benefit of dronabinol for agitation and sleep problems
- Case studies of nabilone, large RCT underway

Van den Elsen, Neurology, 2015
Lui, CNS Drugs, 2015

CHOLINESTERASE INHIBITORS

- Cholinesterase inhibitors may provide some modest benefits in NPS[1]
  - RCTs designed for cognitive outcomes, low baseline NPS
- Apathy, depression, anxiety may be most likely to improve[2]
- Cholinesterase inhibitors may reduce the emergence of certain NPS[3]
  - Apathy, disinhibition, aberrant motor symptoms

1. Raina, Ann Intern Med, 2008
2. Gauthier, Int Psychogeriatr, 2002
3. Cummings, Am J Psychiatry, 2004

CHOLINESTERASE INHIBITORS FOR AGITATION

- Donepezil had no effect in reducing agitation among individuals with significant agitation[1]
- Cholinesterase inhibitors not superior to antipsychotics in treating agitation[2,3]

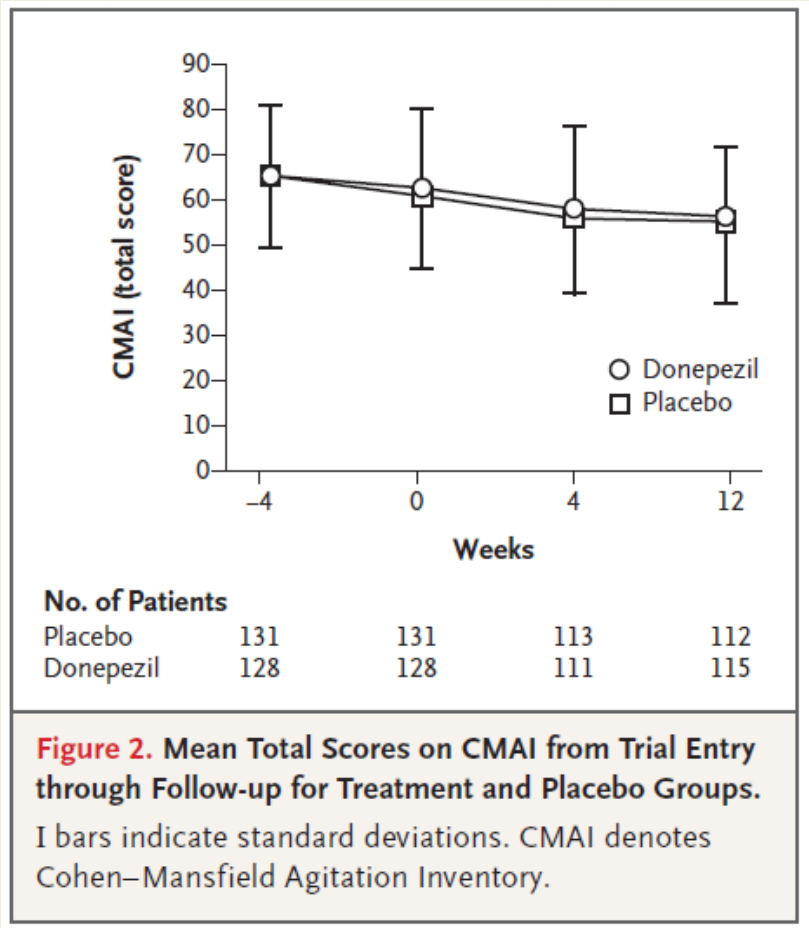


Figure 2. Mean Total Scores on CMAI from Trial Entry through Follow-up for Treatment and Placebo Groups.

I bars indicate standard deviations. CMAI denotes Cohen–Mansfield Agitation Inventory.

1. Howard, *New Eng J Med*, 2007
2. Holmes, Int J Geriatr Psychiatry, 2007
3. Ballard, BMJ, 2005
4. Freund-Levi, Dement Geriatr Cog Disorder, 2014

DEXTROMETHORPHAN/QUINIDINE FOR AGITATION IN DEMENTIA

- Participants with AD and agitation (N=220) treated with DXM/Q 20mg/10mg OD → 30 mg/10mg BID X 5w
- Change in NPI Agitation/Aggression score DXM/Q vs Placebo: -1.5 (95%CI: -0.7 to 2.3, P<0.001)
  - NPI total score: -3.8 to -4.2
- Increased risk of falls (9% vs 4%), diarrhea (6% vs 3%), UTIs (5% vs 4%) and dizziness (5% vs 2%)
- No change significant changes noted in cognition, functioning during treatment

1. Cummings, JAMA, 2015

ANTIDEPRESSANTS FOR DEPRESSION IN DEMENTIA

- Antidepressants for depression in dementia failed to find statistically significant benefit over placebo[1]:
  - Response OR (95% CI): 2.12 (0.95 – 4.70)
  - Remission: 1.97 (0.85 – 4.55)
  - Adverse event rates were relatively low 9% vs. 6% with placebo

1. Nelson, J Am Geriatr Soc, 2011
2. Carmargos, Am J Geriatr Psychiatry, 201

MEDICATIONS FOR SLEEP IN DEMENTIA

- Melatonin most extensively studied, inconclusive[1]
- RCT of trazodone 50 mg or placebo for AD patients with sleep disturbance (N=30)
  - Trazodone improved sleep duration by 42.5 minutes and 8.5% increase in nighttime sleep
  - No significant cognitive or other adverse events noted between groups

1. De Jonghe, Int J Geriatr Psychiatry, 2010
2. Carmargos, Am J Geriatr Psychiatry, 2014

APATHY

- Cholinesterase inhibitors may be associated with improvements in apathy[1,2]
- Recent trial of methylphenidate (10 – 20 mg daily) demonstrated significant reduction in apathy with 21% of treated patient significantly improved compared to 3% of placebo(P=0.02)[3]
- Limited evidence for any other medications

1. Berman, Am J Geriatr Psychiatry, 2012
2. Cummings, Am J Psychiatry, 2004
3. Rosenberg, J Clin Psychiatry, 2013

Choosing Wisely Canada

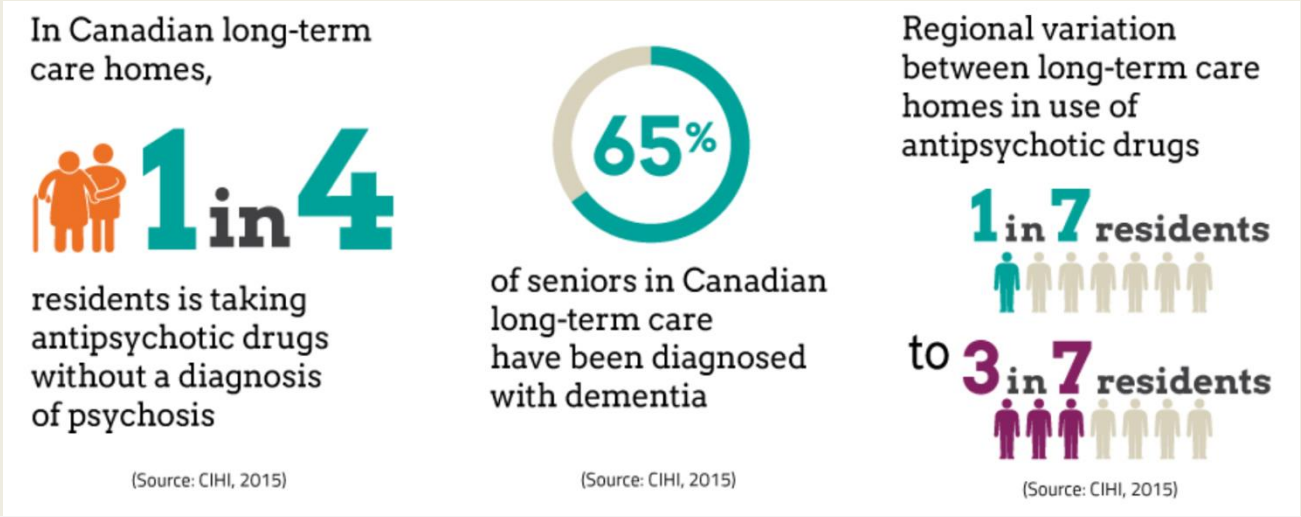
Canadian Geriatrics Society

4 Don't use antipsychotics as first choice to treat behavioural and psychological symptoms of dementia.

People with dementia often exhibit aggression, resistance to care and other challenging or disruptive behaviours. In such instances, antipsychotic medicines are often prescribed, but they provide limited benefit and can cause serious harm, including premature death. Use of these drugs should be limited to cases where non-pharmacologic measures have failed and patients pose an imminent threat to themselves or others. Identifying and addressing causes of behaviour change can make drug treatment unnecessary.

www.choosingwiselycanada.org

PREVALENCE OF ANTIPSYCHOTIC USE



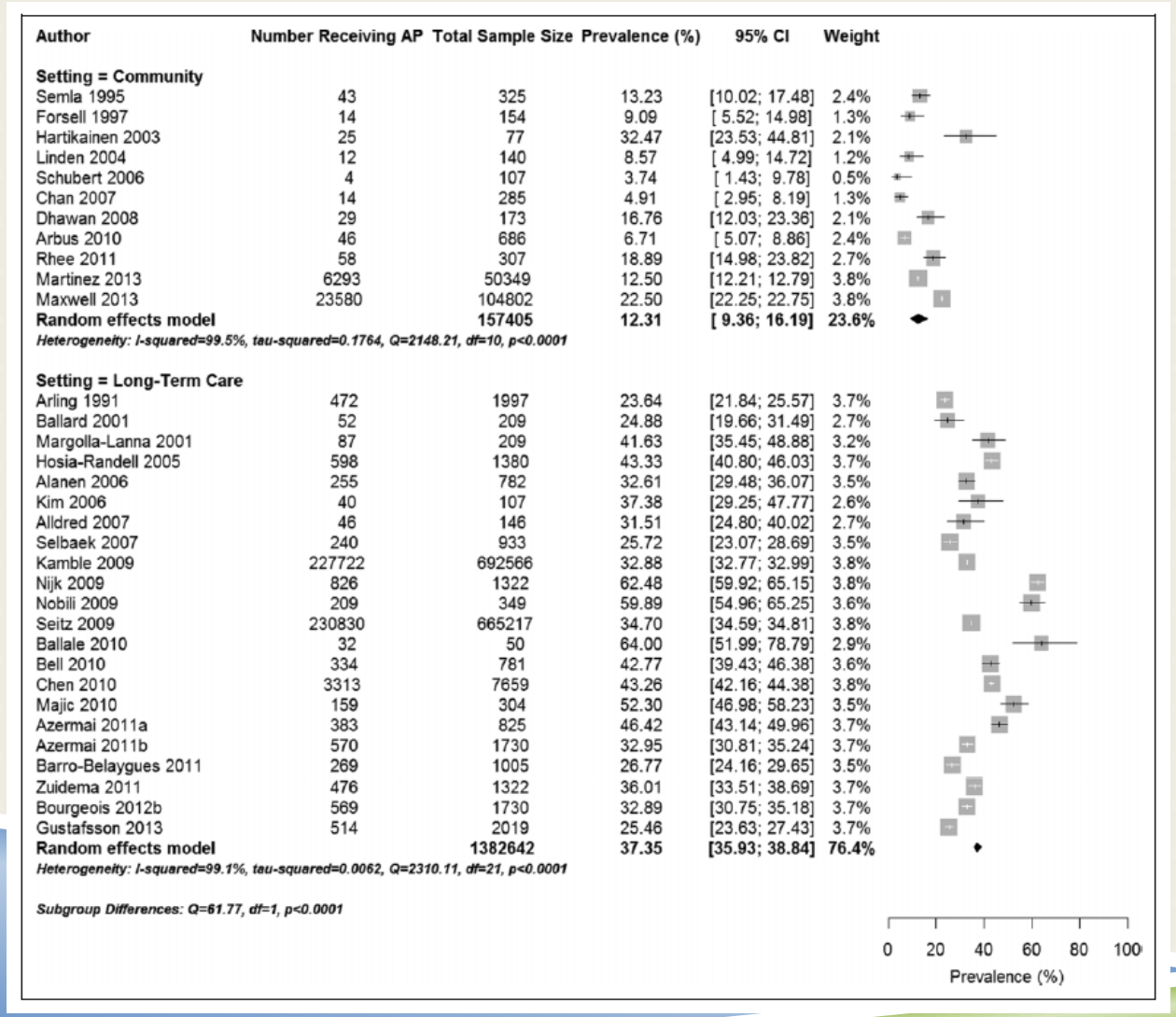
Above average Same as average Below average

Can.	B.C.	Alta.	Sask.	Man.	Ont.	N.B.	N.S.
23.9%	28.0%	18.1%	29.1%	NA	22.9%	NA	NA

N.L.	Y.T.
37.5%	25.6%

http://yourhealthsystem.cihi.ca/

META-ANALYSIS OF ANTIPSYCHOTIC PRESCRIBING IN DEMENTIA



Author	Number Receiving AP	Total Sample Size	Prevalence (%)	95% CI	Weight
Setting = Community					
Semla 1995	43	325	13.23	[10.02; 17.48]	2.4%
Forsell 1997	14	154	9.09	[5.52; 14.98]	1.3%
Hartikainen 2003	25	77	32.47	[23.53; 44.81]	2.1%
Linden 2004	12	140	8.57	[4.99; 14.72]	1.2%
Schubert 2006	4	107	3.74	[1.43; 9.78]	0.5%
Chan 2007	14	285	4.91	[2.95; 8.19]	1.3%
Dhawan 2008	29	173	16.76	[12.03; 23.36]	2.1%
Arbus 2010	46	686	6.71	[5.07; 8.86]	2.4%
Rhee 2011	58	307	18.89	[14.98; 23.82]	2.7%
Martinez 2013	6293	50349	12.50	[12.21; 12.79]	3.8%
Maxwell 2013	23580	104802	22.50	[22.25; 22.75]	3.8%
Random effects model		**157405**	**12.31**	**[9.36; 16.19]**	**23.6%**
Heterogeneity: I-squared=99.5%, tau-squared=0.1764, Q=2148.21, df=10, p<0.0001					
Setting = Long-Term Care					
Arling 1991	472	1997	23.64	[21.84; 25.57]	3.7%
Ballard 2001	52	209	24.88	[19.66; 31.49]	2.7%
Margolla-Lanna 2001	87	209	41.63	[35.45; 48.88]	3.2%
Hosia-Randell 2005	598	1380	43.33	[40.80; 46.03]	3.7%
Alanen 2006	255	782	32.61	[29.48; 36.07]	3.5%
Kim 2006	40	107	37.38	[29.25; 47.77]	2.6%
Alldred 2007	46	146	31.51	[24.80; 40.02]	2.7%
Selbaek 2007	240	933	25.72	[23.07; 28.69]	3.5%
Kamble 2009	227722	692566	32.88	[32.77; 32.99]	3.8%
Nijk 2009	826	1322	62.48	[59.92; 65.15]	3.8%
Nobili 2009	209	349	59.89	[54.96; 65.25]	3.6%
Seitz 2009	230830	665217	34.70	[34.59; 34.81]	3.8%
Ballale 2010	32	50	64.00	[51.99; 78.79]	2.9%
Bell 2010	334	781	42.77	[39.43; 46.38]	3.6%
Chen 2010	3313	7659	43.26	[42.16; 44.38]	3.8%
Majic 2010	159	304	52.30	[46.98; 58.23]	3.5%
Azermai 2011a	383	825	46.42	[43.14; 49.96]	3.7%
Azermai 2011b	570	1730	32.95	[30.81; 35.24]	3.7%
Barro-Belaygues 2011	269	1005	26.77	[24.16; 29.65]	3.5%
Zuidema 2011	476	1322	36.01	[33.51; 38.69]	3.7%
Bourgeois 2012b	569	1730	32.89	[30.75; 35.18]	3.7%
Gustafsson 2013	514	2019	25.46	[23.63; 27.43]	3.7%
Random effects model		**1382642**	**37.35**	**[35.93; 38.84]**	**76.4%**
Heterogeneity: I-squared=99.1%, tau-squared=0.0062, Q=2310.11, df=21, p<0.0001					
Subgroup Differences: Q=61.77, df=1, p<0.0001					

Community: 12%

Long-Term Care: 37%

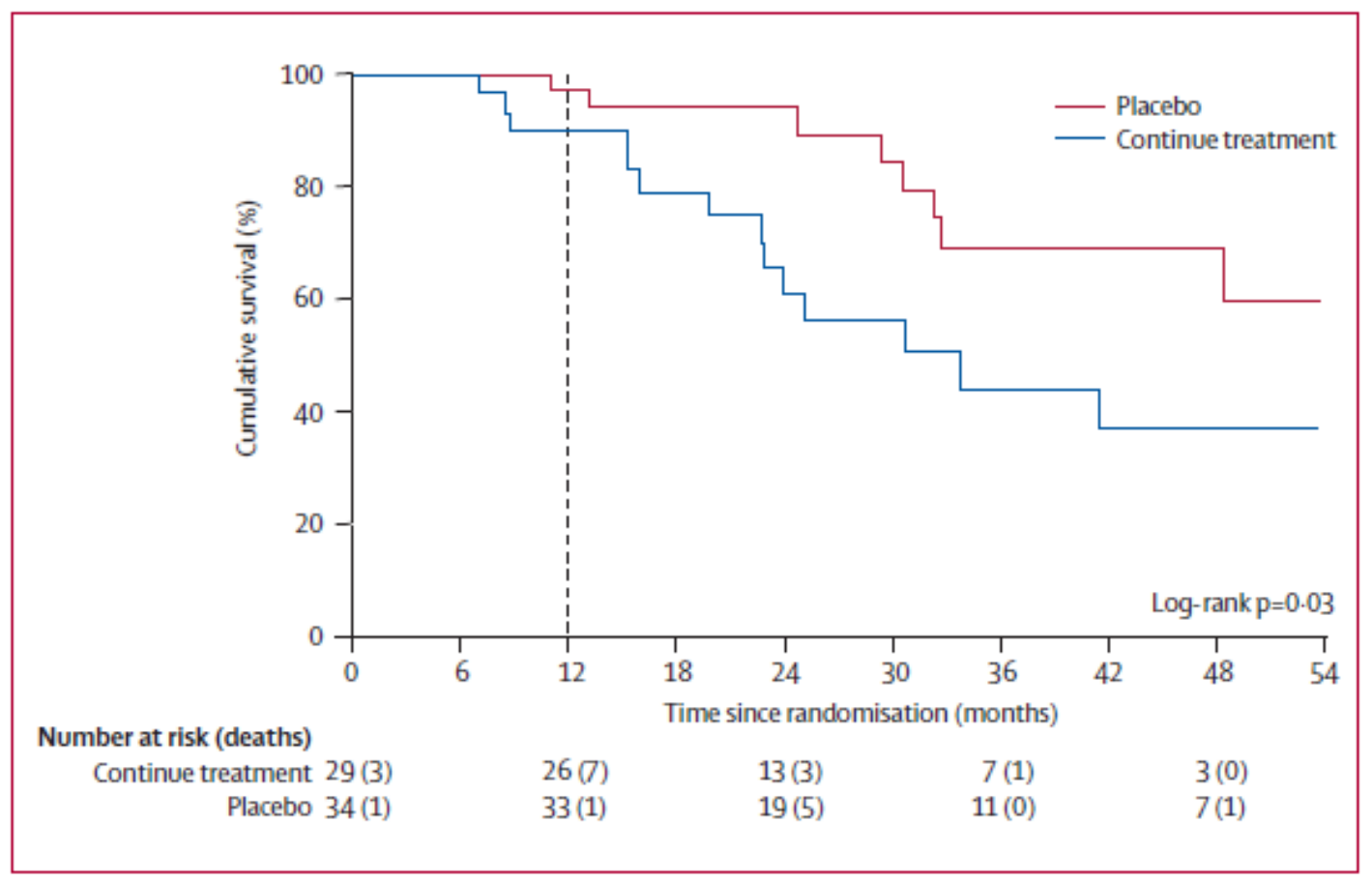
Kirkham, Can J Psychiatry, 2016

DISCONTINUING ANTIPSYCHOTICS

- A large proportion of currently stable individuals on antipsychotics can have antipsychotics safely withdrawn[1,2]
  - Withdrawal associated with 30% increase risk of behavioral worsening compared to placebo [1,2]
- Predictors of successful discontinuation:
  - Less severe NPS at initiation of treatment[2]
  - Lower dose of antipsychotic required to treat NPS[1]

1. Van Reekum, Int Psychogeriatr, 2002
2. Ruths, Int J Geriatr Psychiatry, 2008

EFFECTS OF DISCONTINUING ANTIPSYCHOTICS ON MORTALITY



Ballard, Lancet Neurology, 2009

RELAPSE RISK AFTER ANTIPSYCHOTIC DISCONTINUATION

- Responders to 16 weeks of open label treatment of risperidone were randomized to either continuation or placebo at 16 and 32 weeks
- Relapse rates at 16 weeks following randomization:
  - Risperidone continuation: 23/70 (33%)
  - Placebo: 24/40 (60%)
- Relapse rate at 32 weeks after randomization:
  - Risperidone continuation: 2/13 (15%)
  - Placebo: 13/27 (48%)

1. Devanand, New Eng J Med, 2012

PREDICTORS OF RELAPSE

- Severe hallucinations at baseline associated with greater risk of relapse (HR: 2.96)
  - 77% relapse hallucinations vs. 39% no hallucinations
  - Auditory hallucinations associated with greater risk than visual
  - More severe hallucinations associated with greater risk than less severe hallucinations

Patel, Am J Psychiatry, 2016

STRATEGIES TO REDUCE ANTIPSYCHOTIC USE

- Antipsychotic prescribing can be reduced *on average* by 12 – 20% in LTC homes
  - Most LTC facilities can achieve antipsychotics rates of ~20 - 25%
- Educational materials, educational outreach (academic detailing)
- Most effective when non-pharmacological interventions available
- Several initiatives underway in Canada
- Long-term effectiveness of these strategies are not well known

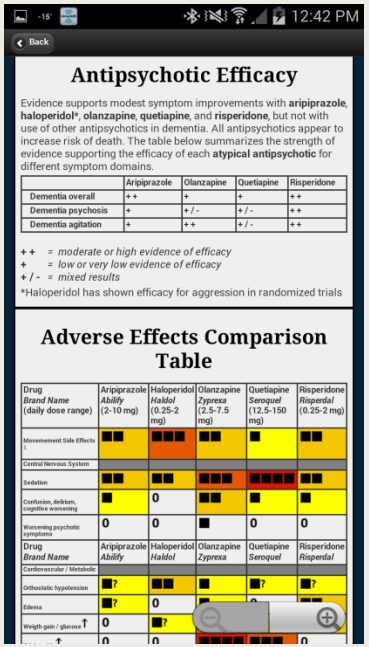
Coon et al., JAMDA, 2014

CONCLUSIONS

- Management of neuropsychiatric symptom in dementia must include thorough assessment of potential contributors to behaviors
- There are several medications that have been demonstrated to be of some benefit in reducing neuropsychiatric symptoms in dementia
- The risks and benefits of starting and continuation of medications for NPS need to be carefully considered for on an individual basis

RESOURCES

- Mobile Applications:
- IA-ADAPT
  - University of Iowa: Improving Antipsychotic Appropriateness in Dementia
  - www.healthcare.uiowa.edu/igec/iaadapt
- BPSD Guide
  - Behavior Management – A Guide to Good Practice, Managing Behavioral and Psychological Symptoms of Dementia (BPSD)



Choosing Wisely Canada
In partnership with the Canadian Medical Association

CGS SCG
Canadian Geriatrics Society

Choosing Wisely Canada is a campaign to help physicians and patients engage in conversations about unnecessary tests, treatments and procedures, and to help physicians and patients make smart and effective choices to ensure high-quality care.

For more information on *Choosing Wisely Canada* or to see other patient materials, visit www.choosingwiselycanada.org.
Join the conversation on Twitter @ChooseWiselyCA

Treating disruptive behaviour in people with dementia

Antipsychotic drugs are usually not the best choice

People with Alzheimer's disease and other forms of dementia can become restless, aggressive, or disruptive. They may believe things that are not true. They may see or hear things that are not there. These symptoms can cause even more distress than the loss of memory.

Doctors often prescribe powerful antipsychotic drugs to treat these behaviours:

- Olanzapine (Zyprexa and generic)
- Quetiapine (Seroquel)
- Risperidone (Risperdal and generic)

If you are uncertain if your loved one is taking one of these medications please ask their health care team.

In most cases, antipsychotics should not be the first choice for treatment, according to the Canadian Geriatrics Society. Here's why:

Antipsychotic drugs don't help much.
Studies have compared these drugs to sugar pills or placebos. These studies showed that

antipsychotics usually don't reduce disruptive behaviour in older dementia patients.

Antipsychotic drugs can cause serious side effects.
Doctors can prescribe these drugs for dementia. However, Health Canada has not approved this use. The side effects can be serious.

Side effects include:

- Drowsiness and confusion—which can reduce social contact and mental skills, and increase falls.
- Weight gain.
- Diabetes.
- Shaking or tremors (which can be permanent).
- Pneumonia.
- Sudden death.

Patient Resources

www.choosingwiselycanada.org

RESOURCES

- Canadian Coalition for Seniors Mental Health
  - www.ccsmh.ca
- Clinician Pocket Card:
  - "Tool on the Pharmacological Treatment of Behavioral Symptoms of Dementia in Long-Term Care"
  - www.cavershambooksellers.com