MANAGEMENT OF NEUROPSYCHIATRIC SYMPTOMS OF DEMENTIA

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FACULTY/PRESENTER DISCLOSURE

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- 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 developments in non-pharmacological and pharmacological treatments for NPS;
- 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]

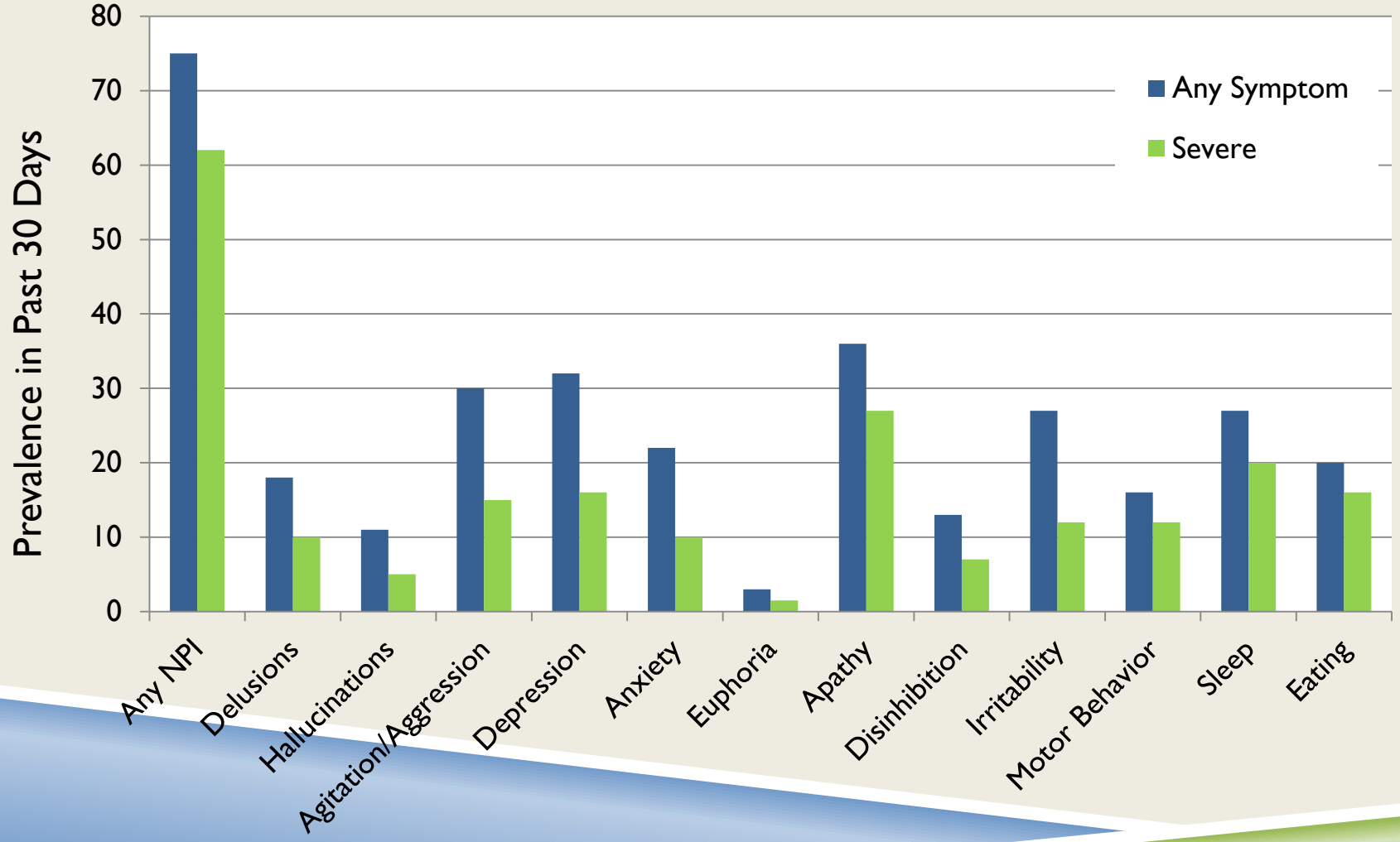
1. Finkel, Int Psychogeriatr, 1996; 8(suppl 3):497-500

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

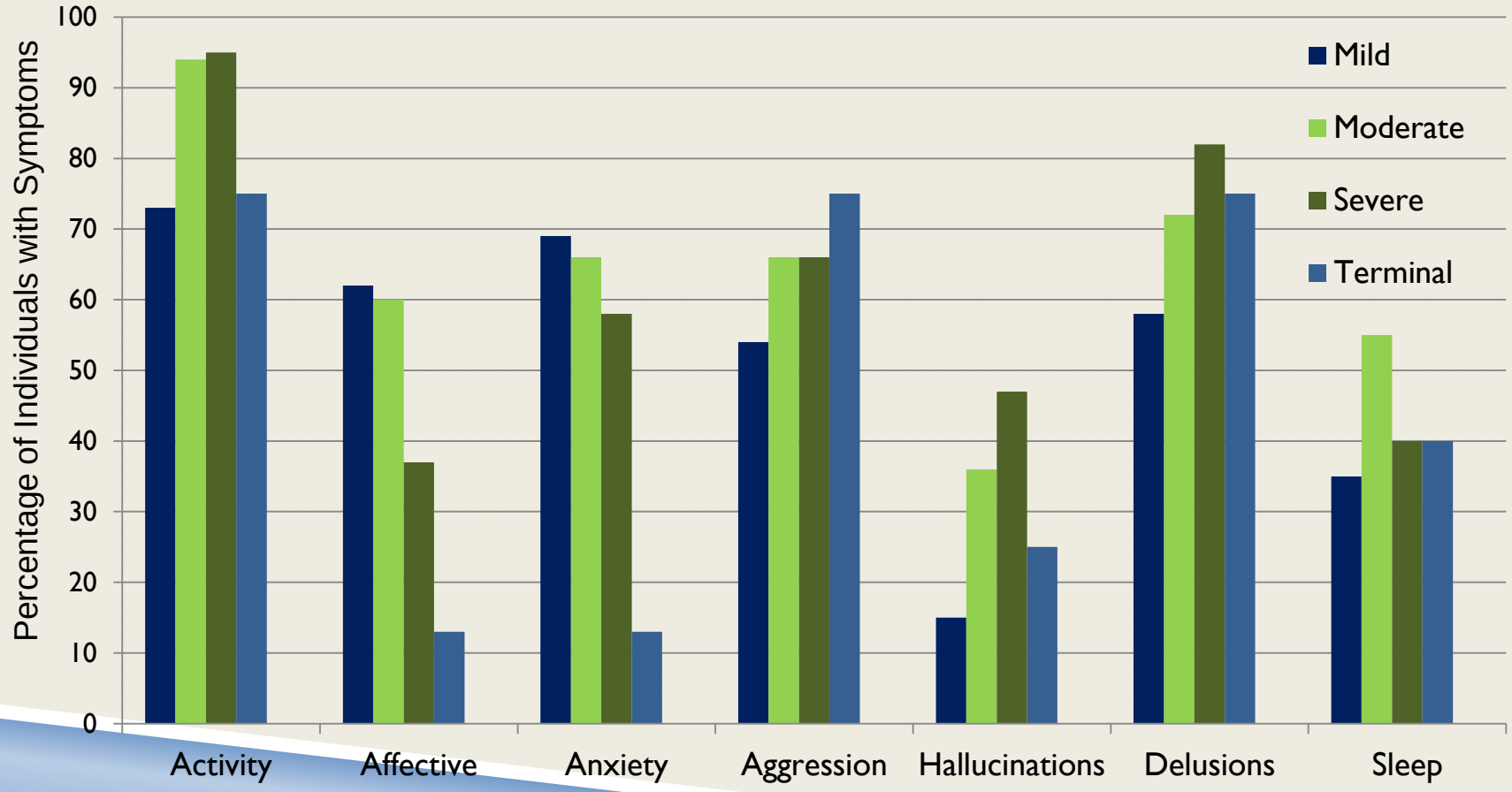
1. Cohen-Mansfield, J Gerontol, 1989

PREVALENCE OF NPS IN ALZHEIMER'S DISEASE



Lyketsos, JAMA, 2002

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

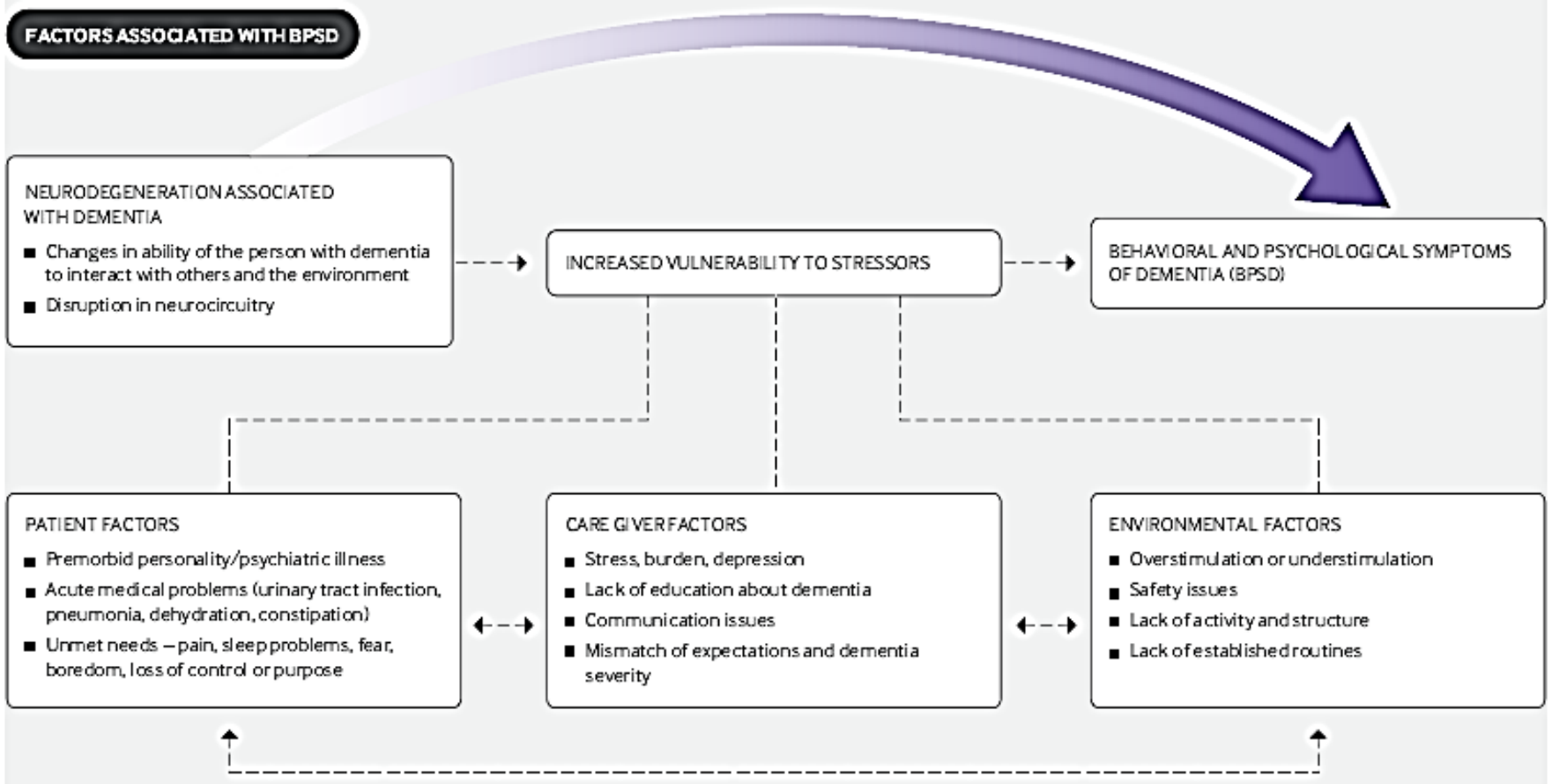
1. Steinberg, Int J Geriatr Psychiatry, 2004
2. Aalten, Int J Geriatr Psychiatry, 2005

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

PSYCHOLOGICAL THEORIES OF NPS

- Lowered Stress Threshold[1]
- Learning Theory[2]
- Unmet needs → Tailored interventions[3]
  - Verbal agitation – pain, depression
  - Physically non-aggressive agitation - stimulation
  - Physically aggressive agitation – avoiding discomfort

1. Hall, Arch Psych Nurs, 1987
2. Cohen-Mansfield, Am J Geriatr Psych, 2001
3. Cohen-Mansfield, Am Care Quarterly, 2000

DICE APPROACH

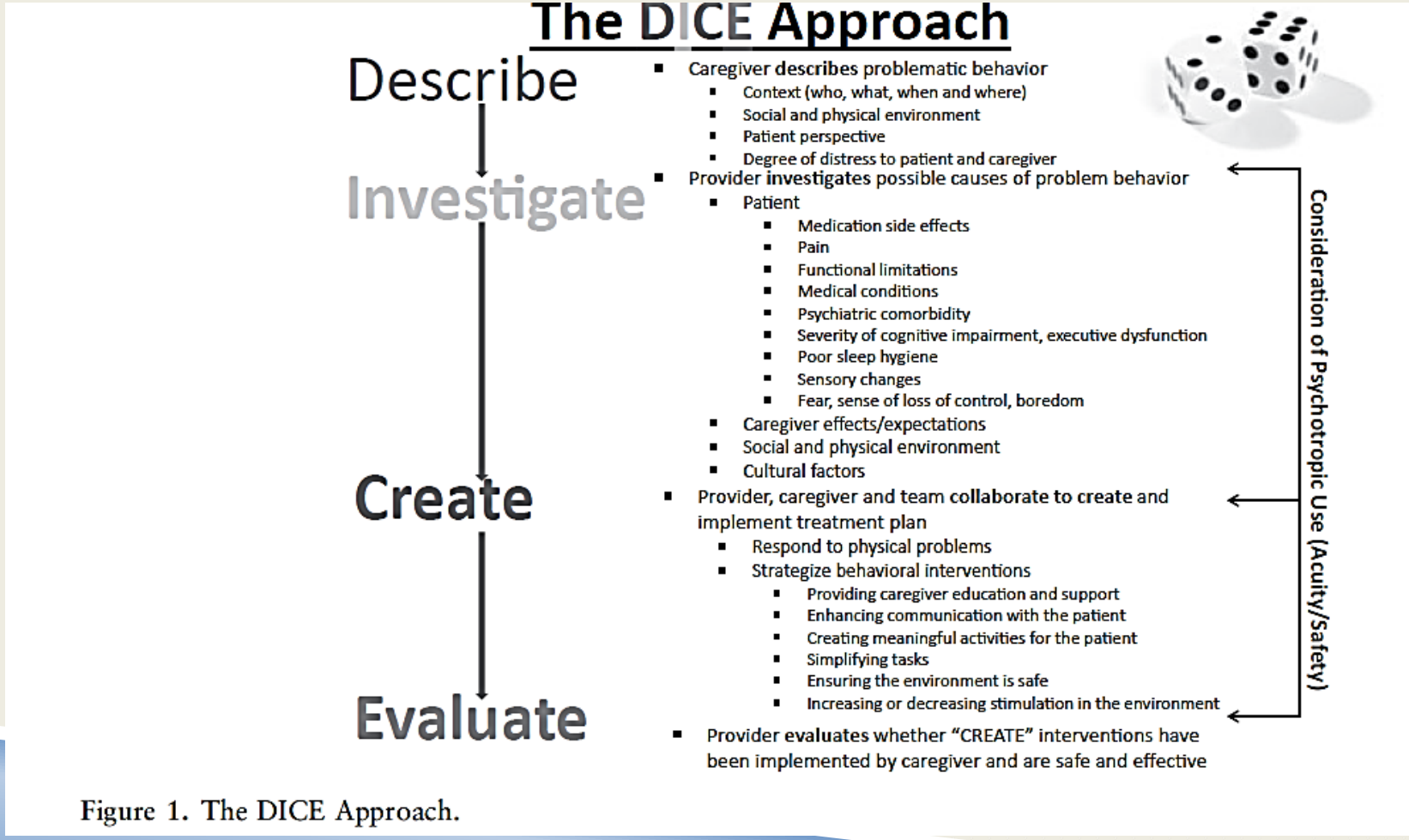
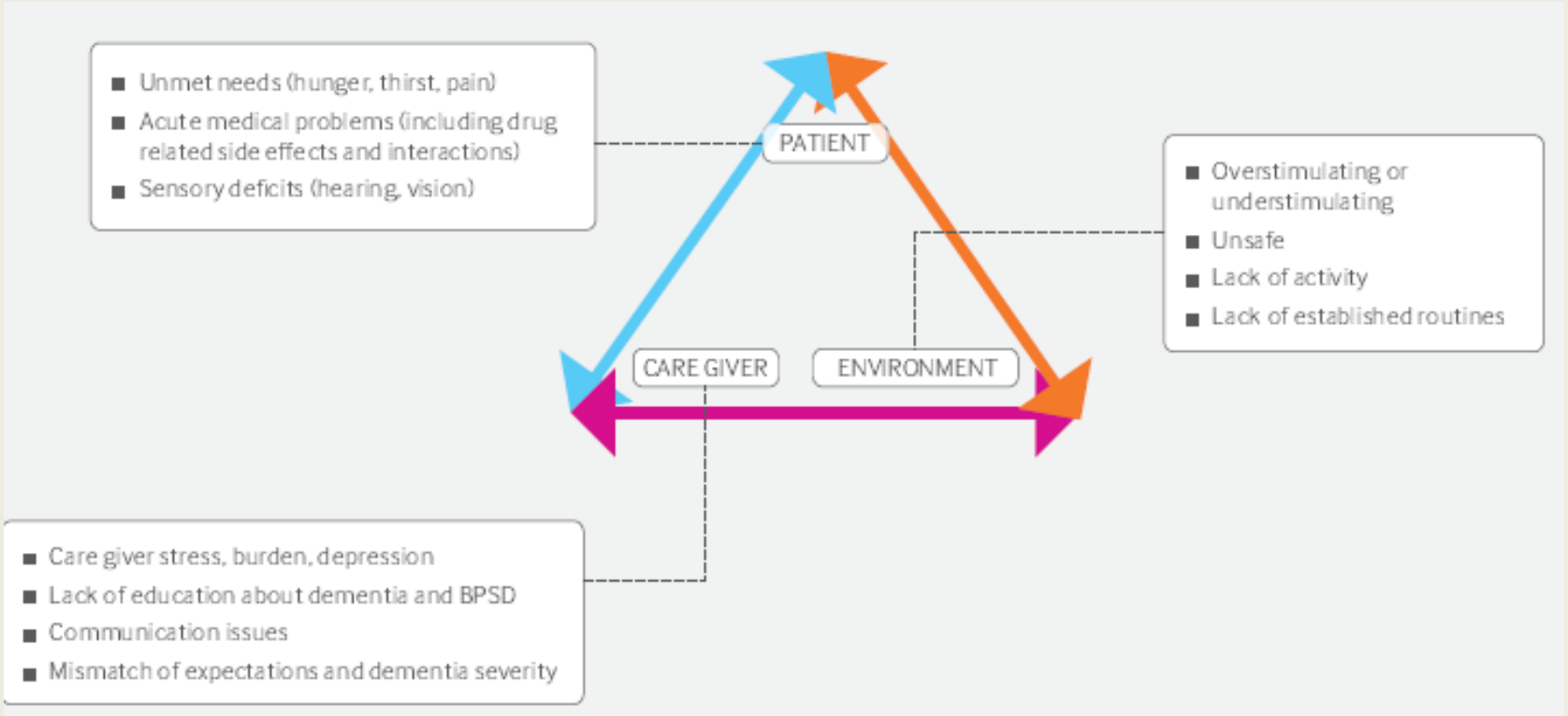


Figure 1. The DICE Approach.

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

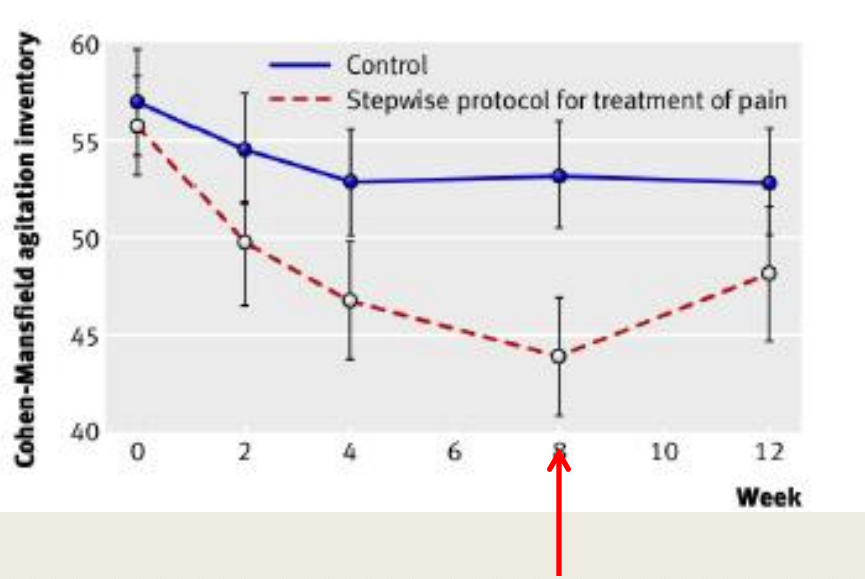
PAIN TREATMENT PROTOCOL

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

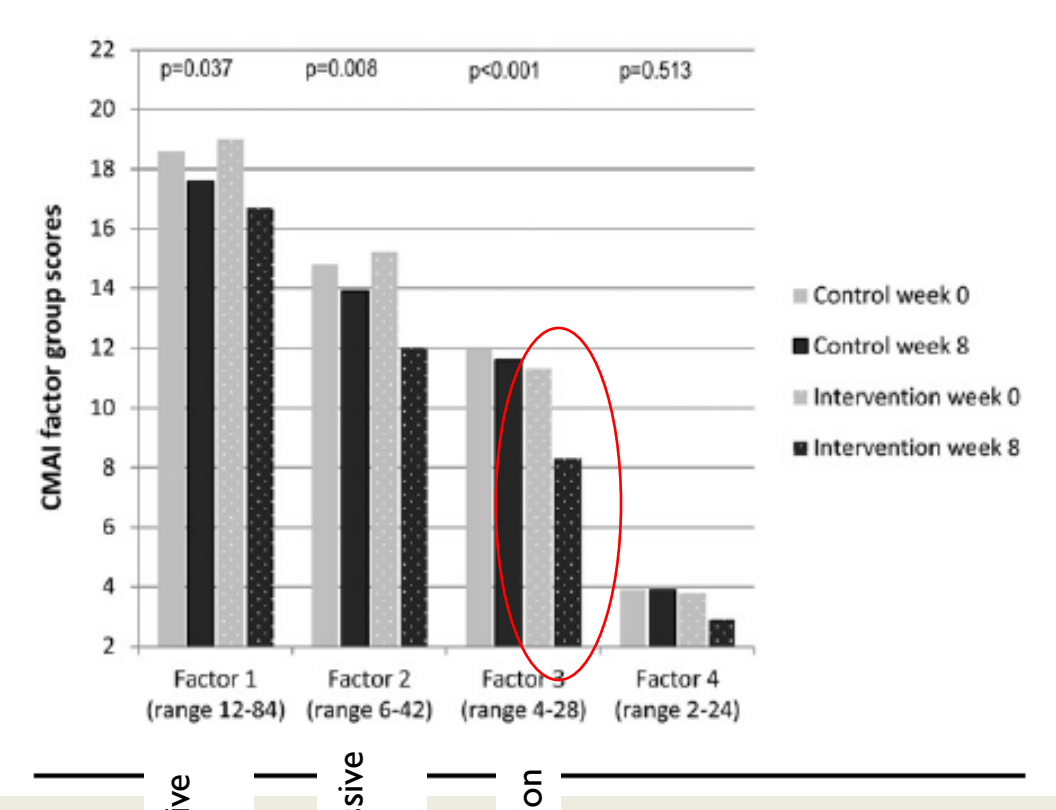


Medications Withdrawn

- 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

PAIN AND AGITATION SYMPTOMS



Husebo, AJGP, 2013

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

TRAINING CAREGIVERS AND STAFF

- Some staff and caregiver training approaches are effective in reducing NPS[1-3]
- Also referred to as patient-centred care
- Most training programs involve education about dementia symptoms
- Communication strategies to avoid confrontation
- Strategies for redirection and distraction
- Often incorporate *personalized* pleasant events into interactions

1. McCallion, *Gerontologist*, 1999
2. Chenoweth, *Lancet Neurology*, 2009
3. Testad, *J Clin Psychiatry*, 2010

PARTICIPATION IN PLEASANT EVENTS

- 1-to-1 interaction with personalized pleasant events has been demonstrated to reduce NPS[1]
  - Given 3X/week – 20 – 30 minutes/session
- Participation in group "validation therapy" may also be beneficial[2]

1. Lichtenberg, *Gerontologist,* 2005
2. Toseland, *J Appl Gerontol*, 1997

EXERCISE

- Exercise programs have been demonstrated to reduce NPS in LTC residents[1-3]
- Training caregivers in behavioral management and exercise program improved physical functioning of person with dementia and depressive symptoms[4]
  - 30 minutes/day was recommended
  - Exercise program included strength, flexibility, aerobic activity, balance

1. Alessi, J Am Geriatr Soc, 1999
2. Landi, Arch Gerontol Geriatr, 2004
3. Williams, Am J Alzheimer Dis Other Dementi, 2007
4. Teri, JAMA, 2003

MUSIC

- Group music with movement or individualized music therapy are effective in reducing NPS[1,2]
- 30 minutes 2 – 3 times/ week
  - May use prior to times of increased agitation
- *Personalized* music more effective than generic music

1. Sung, *Complement Ther Med*, 2006
2. Raglio, *Alzheimer Dis Assoc Disord*, 2008

SENSORY STIMULATION

- Therapeutic touch or gentle massage may relieve symptoms of agitation[1,2]
- Snoezelen (multisensory stimulation) providing tactile, light, olfactory, or auditory stimulation[3]
- Aromatherapy with massage
  - 1 positive[4] and 1 negative[5] RCT

1. Hawranik, *West J Nurs Pract*, 2008
2. Woods, *Alter Ther Health Med*, 2005
3. Van Weert, *J Am Geriatr Soc*, 2005
4. Ballard, *J Clin Psychiatry*, 2002
5. Burns, *Dementia Geriatr Cogn Disord*, 2011

LIMITATIONS OF PSYCHOSOCIAL TREATMENTS

- Modest effects of treatments
- Effectiveness for aggression and psychosis may be limited
  - Agitation, depressive symptoms, apathy may be more likely to respond
- May required prolonged and sustained implementation for effects to be realized
- Many interventions have only been evaluated in small studies, methodological quality is limited

FEASIBILITY OF NON-PHARMACOLOGICAL INTERVENTIONS

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
- 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

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

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

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

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

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

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

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 and haloperidol

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

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]

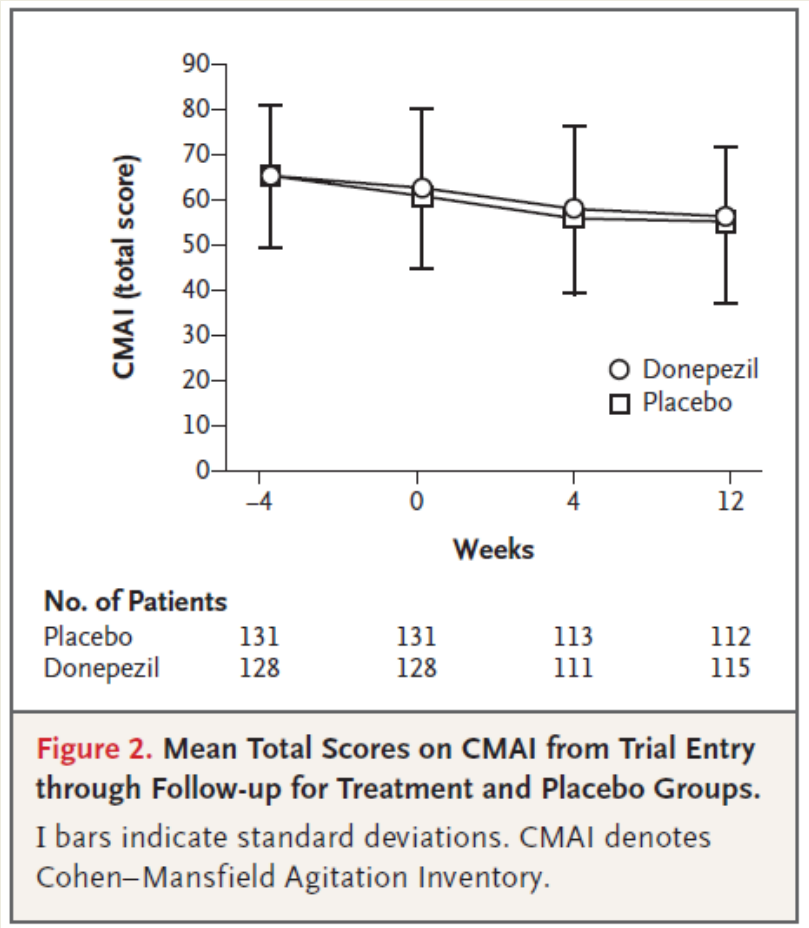


Figure 2. Mean Total Scores on CMAI from Trial Entry through Follow-up for Treatment and Placebo Groups.

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

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

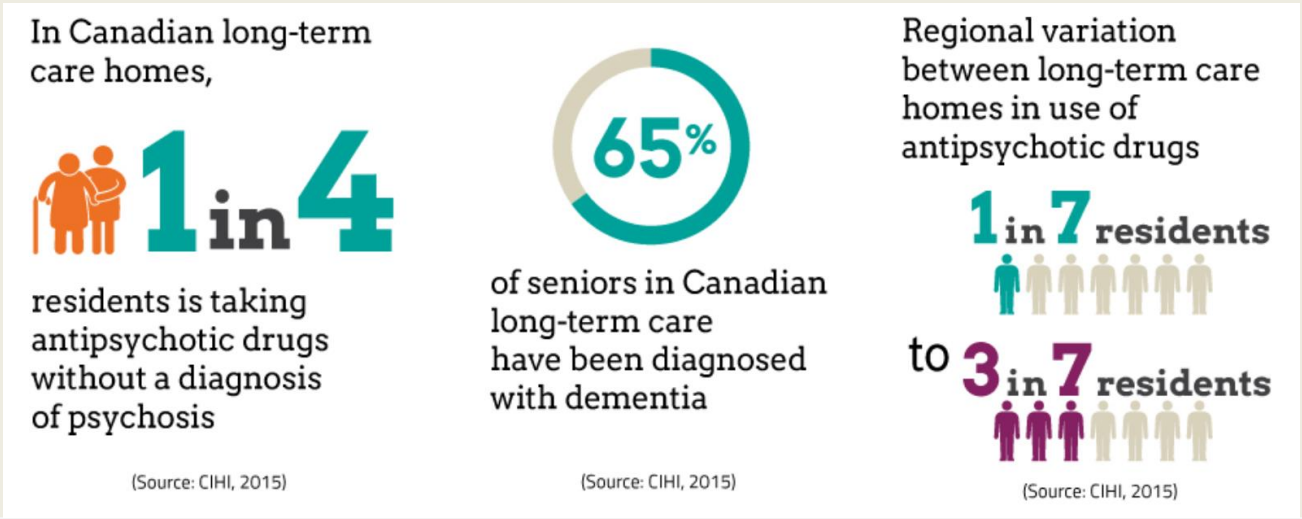
Canadian Geriatrics Society

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%

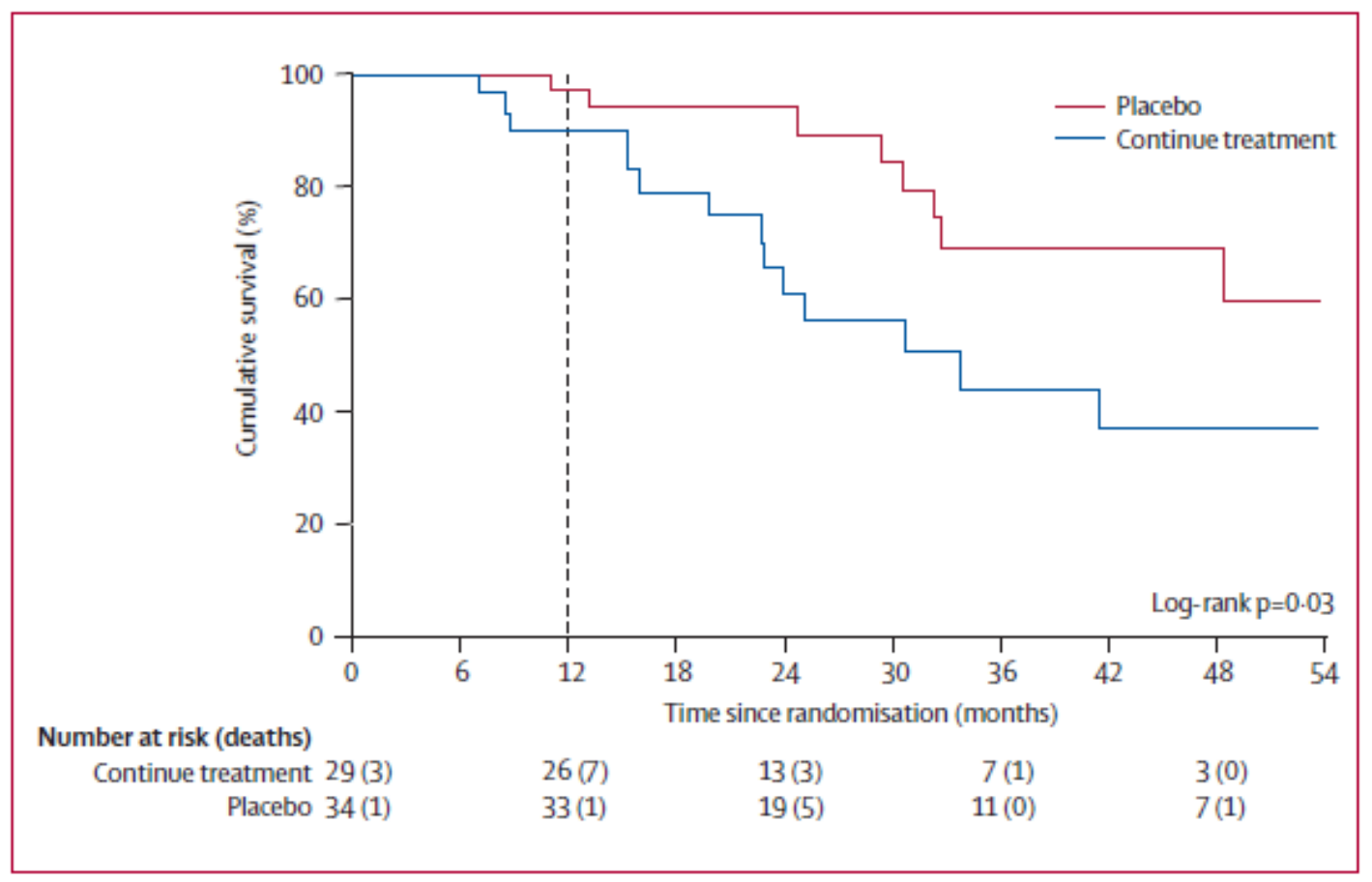
http://yourhealthsystem.cihi.ca/

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
- Non-pharmacological interventions have increasing evidence to support their use
- The risks and benefits of starting and continuation of medications for NPS need to be carefully considered for on an individual basis