# MANAGEMENT OF NEUROPSYCHIATRIC SYMPTOMS OF DEMENTIA: A TREATMENT UPDATE

Union Hospital Grand Rounds
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NO FINANCIAL DISCLOSURES

100% OF SALARY COMES FROM INDIANA UNIVERSITY AND IU HEALTH PHYSICIANS

WE WILL BE DISCUSSING OFF LABEL USE OF PSYCHOTROPIC MEDICATIONS TO TREAT DEMENTIA

# OBJECTIVES

- Demonstrate an understanding of the morbidity and mortality associated with Neuropsychiatric Symptoms (NPS) of dementia
- Integrate non-pharmacologic management of NPS into clinical practice
- Appreciate the potential risks and benefits of pharmacologic management of NPS

# CASE: MRS. D

- 51 y/o woman presents to hospital with reduced comprehension, memory impairment, disorientation and communication difficulties (aphasia).
- Paranoia

  "*One of her 1st symptoms was jealousy of her husband. At times she thought that someone was trying to kill her.*"
- Auditory Hallucinations

  *"Just now a child called, is he there?"*
- Agitation

  *"During her stay she became agitated, screamed, was non-cooperative; showed great fear and repeated "I will not be cut. I do not cut myself."*

*Maurer et al. Lancet 1997;349:1546–49*

# CASE: MRS. D

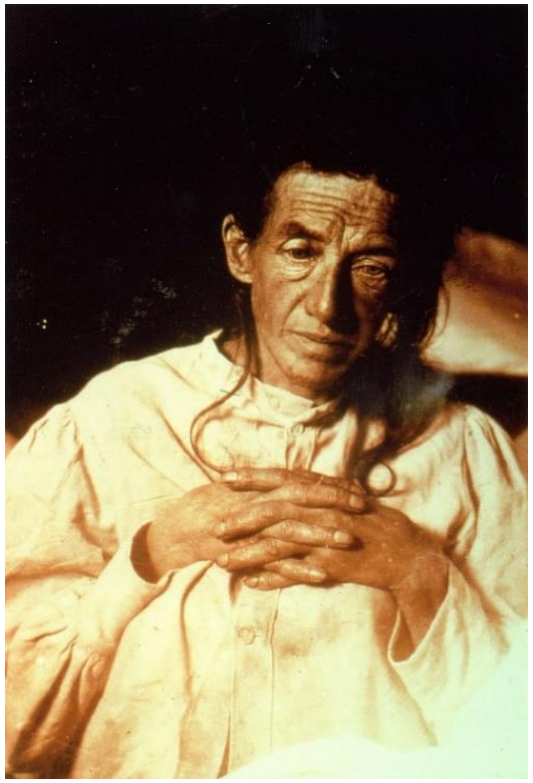
- Inpatient work up: no evidence of delirium, risky medications, or other medical illness to explain dx
- Dx: Alzheimer's disease
- You meet with her husband
- What do you want to know?
- What recommendations do you have for the husband?
- What medication options would you consider?

# WHAT HAPPENED TO MRS. D?

- She developed a decubitus ulcer at the sacral and left trochanteric area of 5 cm.
- Very weak, high fever up to 40°C
- Pneumonia in both inferior lobes
- After 4.5 years of illness she passed away

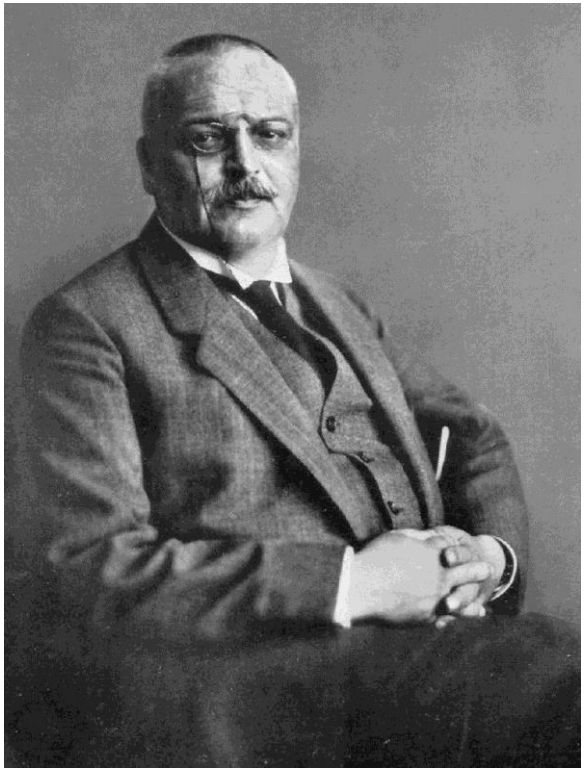
When did she die?

*Admitted: 11/25/01*
*Died: 4/8/1906*



*Maurer et al. Lancet 1997;349:1546–49*

# ALOIS ALZHEIMER



*Maurer et al. Lancet 1997;349:1546–49*

# PROBABLE DIAGNOSIS OF ALZHEIMER'S DISEASE (AD)

**Meets criteria for dementia**

**A. Insidious onset**

**B. Clear-cut history of worsening cognition by report or observation**

**C. The initial and prominent cognitive deficits fit in 1 of the following categories:**

**1) Amnestic Presentation (learning & recall deficits, dysfunction in other cognitive domain)**

**2) Non-Amnestic Presentation**

**Language**

**Visuospatial**

**Executive dysfunction**

*McKhann et al. Alzheimers Dementia. 2011;7(3):263–9.*

# CRITERIA FOR ALL CAUSE DEMENTIA

A. **Impaired Function in Activities**
B. **Decline from Prior Function**
C. **Cognitive and Behavioral Problems (at least in 2 Domains)**
    1. Recall/Memory
    2. Reasoning, Handling complex tasks, and Judgment
    3. Visuospatial Abilities
    4. Language Functions (speaking, reading, writing)
    5. Changes in Personality and Behavior

*McKhann et al. Alzheimers Dementia. 2011;7(3):263–9.*

# THEORIES UNDERLYING AGITATION

Model I: Direct impact of dementia

Model II: Unmet needs

Model III: Behavioral model

Model IV: Environmental Vulnerability

Model V: Progressively Lowered Stress Threshold Model (PLST)

*Cohen-Mansfield. "Agitation in the Elderly: Definitional and Theoretical Conceptualizations" Agitation in Patients with Dementia. 2003*

# MODEL I: DIRECT IMPACT OF DEMENTIA

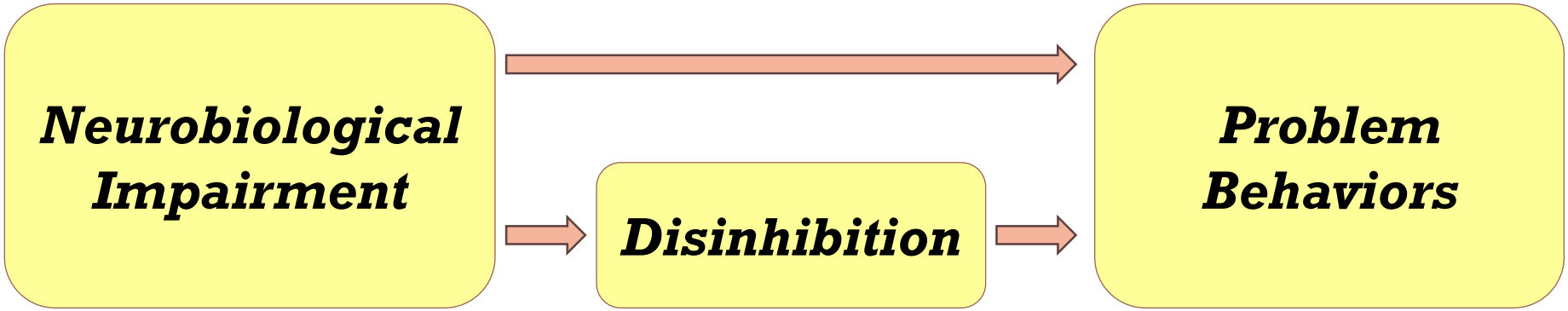



*Figure 1-2. Reproduced from Cohen-Mansfield. "Agitation in the Elderly: Definitional and Theoretical Conceptualizations" Agitation in Patients with Dementia. 2003*

# MODEL II: UNMET NEEDS

- Pain & physical discomfort
- Sleep disturbance
- Mental discomfort: depression, anxiety
- Social contact
- Uncomfortable environmental conditions.
- Level of stimulation

*Figure 1-3. Reproduced from Cohen-Mansfield. "Agitation in the Elderly: Definitional and Theoretical Conceptualizations" Agitation in Patients with Dementia. 2003*

# MODEL III: BEHAVIORAL

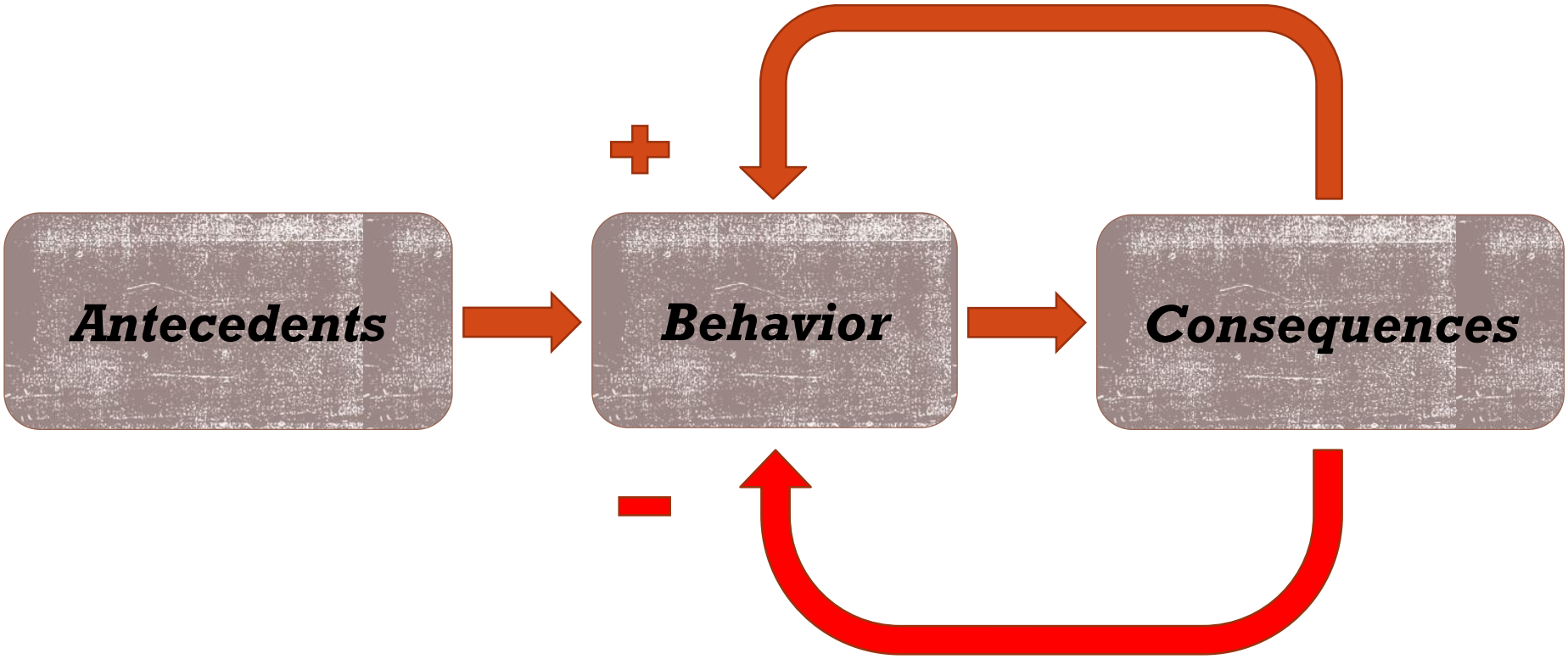



*Figure 1-4. Reproduced from Cohen-Mansfield. "Agitation in the Elderly: Definitional and Theoretical Conceptualizations" Agitation in Patients with Dementia. 2003*

# MODEL IV: ENVIRONMENTAL VULNERABILITY

# MODEL V: PROGRESSIVELY LOWERED STRESS THRESHOLD MODEL (PLST)

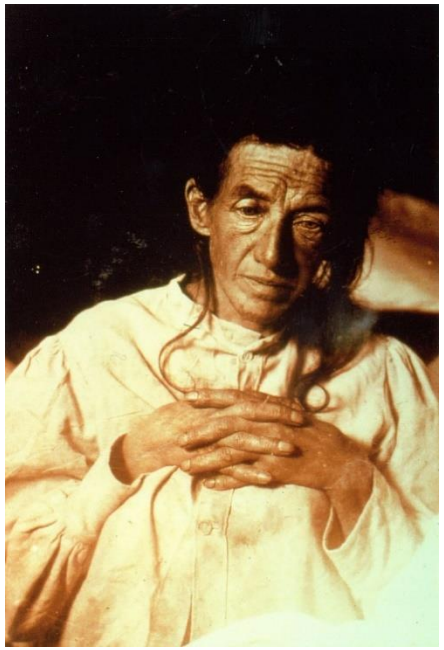
- Dementia leads to impaired ability to receive, process and respond to stimuli.
- Impairments worsen as the illness progresses.
- Persons with dementia have difficulty in tolerating stressors, which leads to problematic behaviors.

*Hall et al. Arch of Psychiatric Nursing. 1987*
*Warchol et al. 2010*

# NEUROPSYCHIATRIC SYMPTOMS (NPS) OF DEMENTIA

The "Non-cognitive" symptoms of dementia

AKA, "Behavioral and Psychological Symptoms of Dementia (BPSD)"



*Auguste D,*
*Photo: November 1902*

# NEUROPSYCHIATRIC SYMPTOMS (NPS) OF DEMENTIA

Socially Inappropriate Behaviors

Catastrophic Reaction

Agitation

Physical Aggression

Verbal Aggression

Restlessness

Wandering

Shadowing

Insomnia

Sundowning

Anxiety

Apathy

Depression

Irritability

Hallucinations

Delusions

Personality Changes

Sexual Disinhibition

Hoarding

Increased Impulsivity

# NEUROPSYCHIATRIC SYMPTOMS (NPS) OF DEMENTIA

Associated with:

- Caregiver burden ↑
- Psychotropic medication use ↑
- Quality of life ↓
- Economic costs ↑
- Function ↓
- Rate of disease progression ↑
- Earlier nursing home placement ↑

*As many as 97% experience BPSD in the course of dementia*

*Peters et al 2015, Fischer et al 2012, Gaugler et al 2009, Rabins et al 2013, Steinberg 2008*

# PSYCHOTIC SYMPTOMS (DELUSIONS)

**Delusion:** "A false belief based on incorrect inference about external reality that is firmly sustained despite what almost everybody else believes and despite what constitutes incontrovertible and obvious proof or evidence to the contrary."

- 43% of AD patients have delusions in one study (n=209, Deutsch)
- Delusions predict aggression
- 80% of dementia patients with physical aggression had delusions (52wk, n=270, Gilley)

*Gilley, D.W., et al. J Am Geriatr Soc, 1997. 45(9): p. 1074-9.*
*Deutsch, L.H., et al. Am J Psychiatry, 1991. 148(9): p. 1159-63.*
*International Psychogeriatrics. Behavioral and Psychological Symptoms of Dementia Slide Kit 2015*

# PSYCHOTIC SYMPTOMS (HALLUCINATIONS)

**Hallucination**: defined as the perception of an object or event (in any of the 5 senses) in the absence of an external stimulus

- Frequency in Dementia 12-49%
- Visual hallucinations most common 30% of patients with dementia
- Auditory hallucinations up to 10%
- Lewy body dementia up to 80% of patients have visual hallucinations
- Hallucinations **did not** predict physical aggression

Gilley, D.W., et al. J Am Geriatr Soc, 1997. 45(9): p. 1074-9.
*Teeple RC, Caplan JP, Stern TA. Visual hallucinations: differential diagnosis and treatment. Primary care companion to the Journal of clinical psychiatry*

# DEMENTIA AND DEPRESSION

- Subjects with late life depressive symptoms had a 2 fold increased risk to develop Alzheimer's disease (AD)
- Depression that develops in late life sometimes represents an AD prodrome.
- Major Depressive disorder affects 25 to 50% of patients with Alzheimer's Dementia (AD).

*Barnes DE Arch Gen Psychiatry 2012*

# AGITATION DEFINITION WORK GROUP

- In 2015, International Psychogeriatric Association (IPA) developed a provisional consensus definition of agitation as:

1. Occurring in a cognitive disorder or dementia
2. Exhibiting behavior consistent with emotional distress
3. Manifesting excessive motor activity, verbal aggression or physical aggression
4. Causing excess disability and not attributable to another disorder (J. Cummings et al., 2015).

- Agitation increases as cognitive impairment increases and dementia progresses.

# TYPES OF AGITATION

**TABLE 2. Subtypes of Agitation**

Physically nonaggressive behaviors
- General restlessness
- Repetitious mannerisms
- Pacing
- Trying to get to a different place
- Handling things inappropriately
- Hiding things
- Inappropriate dressing or undressing

Physically aggressive behaviors
- Hitting
- Pushing
- Scratching
- Grabbing things
- Grabbing people
- Kicking and biting

Verbally nonaggressive behaviors
- Negativism
- Does not like anything
- Constant requests for attention
- Verbal bossiness
- Complaining or whining
- Relevant interruptions
- Irrelevant interruptions
- Repetitive sentences

Verbally aggressive behaviors
- Screaming
- Cursing
- Temper outbursts
- Making strange noises

Cohen-Mansfield. International Psychogeriatrics, Vol. 8, Suppl. 3, 1996

# AGITATION BY DEMENTIA TYPE

## Alzheimer's Disease

- Mild AD 10 - 47%
- Moderate AD 40 – 55%
- Severe AD 62.5 – 85%

## Vascular Dementia

- Very similar in agitation incidence to AD

*Picture from http://www.wisegeek.com/what-is-vascular-dementia.htm*

## Frontotemporal Dementia

- More aberrant motor behavior, disinhibition and apathy

*Mega et al 1996, Eisdorfer et al 1992, Senanarong et al, 2004; Srikanth et al 2005*
*Barkin and Mintzer. "Epidemiology of Agitation" Agitation in Patients with Dementia. 2003*
*International Psychogeriatrics BPSD Slide Kit 2015*

# ASSESSMENT OF NPS:

- Direct interview
- Direct observation
- Proxy report
- Measurements and scales
- Need for accurate descriptions
- Think of sensory impairment
- **Think of physical illness**
- **Think of mental illness**
- **Review for anticholinergic or contributing medications**

# ASSESSMENT OF NPS:

- Identify what symptom(s) causes the greatest concern
- Describe each symptom in detail
- ABCs: Specify the Antecedents of Behaviors (triggers) and their Consequences (makes better or worse).
- Keep a written diary or graph: hour to hour or by shift.

# QUESTIONS TO ASK

- Does this symptom warrant medication treatment? Why?
- Is the symptom or behavior likely to respond to pharmacotherapy?
- Which class of medications would be best?
- What are side effects of the medication?
- How long should treatment last?

# ASSESSMENT OF NPS:

One symptom at a time:

- What exactly is the symptom?
- When? Where? With whom?
- How long does it last?
- How does it impact others?
- What makes it better or worse?

*O'Connor, Rabins, Swanick et al. "Module -5 Non-Pharmacologic Treatments for BPSD" 2011 International Psychogeriatric Association.*

# NPS TREATMENT:

**Only start medications when:**

- Physical causes of symptoms are ruled out
- Environmental factors are not a cause
- Side effects of other medications are not a cause
- **Symptoms have not responded to non-pharmacologic interventions**

*Bohac, McNeilly, Folks. "Use of Behavioral Assessment Scales for Evaluating Agitation in Dementia" Agitation in Patients with Dementia. 2003*

# NPS TREATMENT:

- Clearly identify target behavior
- Treatment should be time limited
- All psychotropic medications should be reviewed every 3 months
- Should monitor for benefits and side effects

*Bohac, McNeilly, Folks. "Use of Behavioral Assessment Scales for Evaluating Agitation in Dementia" Agitation in Patients with Dementia. 2003*

# IS TREATMENT HELPFUL?

- Measure symptoms to see if treatment is working.
- Set realistic small goals.
- Continually reassess, reevaluate
- Have a future plan.

*O'Connor, Rabins, Swanick et al. "Module -5 Non-Pharmacologic Treatments for BPSD" 2015 IPA.*
*Long, SW. Caring for People with Challenging Behaviors. Health Professions Press. 2010*

# WHAT DOES THE EVIDENCE SAY?

## An overview of systematic reviews of pharmacological and non-pharmacological interventions for the treatment of behavioral and psychological symptoms of dementia

Suzanne M. Dyer,[1,2] Stephanie L. Harrison,[1,2] Kate Laver,[1,2] Craig Whitehead[1,2] and Maria Crotty[1,2]

[1] *Department of Rehabilitation, Aged and Extended Care, Faculty of Medicine, Nursing and Health Sciences, School of Health Sciences, Flinders University, Level 1, C Block, Repatriation General Hospital, Daw Park, SA, Australia*
[2] *NHMRC Cognitive Decline Partnership Centre, The University of Sydney, Sydney NSW, Australia*

*Dyer SM et al. Int Psychogeriatr. November 2017:1-15.*

# AN OVERVIEW OF SYSTEMATIC REVIEWS

- Looked at Systematic Reviews of RCTs of both pharm and non-pharm interventions for NPS
- Search 2015 – Cochrane Database, DARE, Medline, EMBASE, PsycINFO
- PRISMA
  - After duplicates removed (n=2495)
  - Excluded (n=2191)
  - Full text reviewed (n=304)
  - 15 studies included

*Dyer SM et al. Int Psychogeriatr. November 2017:1-15.*

# NON-PHARM NPS REVIEWS

**Table 1.** Characteristics of included systematic reviews

| REVIEW | DATE OF SEARCH | POPULATION CRITERIA, AGE & DEMENTIA SEVERITY OF INCLUDED STUDIES. | INTERVENTION | COMPARISON | OUTCOMES (MEASUREMENT SCALES USED) | QUALITY APPRAISAL (AMSTAR) |
|---|---|---|---|---|---|---|
| *Non-pharmacological interventions* | | | | | | |
| Cook *et al.* (2012) | March 2011 | Dementia of any type with BPSD receiving support or treatment from mental health workers, care staff, family, or other caregivers.<br>Mean age 74.8–85.<br>Mean MMSE 12.6–16.8. | Functional analysis-based interventions (formulation-led individualised interventions aimed at identifying unmet need/cause/antecedents and consequences of behaviour "ABCs") | Usual care | Frequency of problem behaviours (change in PC, RAGE, RMBPC, CMAI, MBCL) | 11/11 |
| Forbes *et al.* (2015) | October 2013 | Majority ≥65 years, dementia diagnosis.<br>Mean age 83<br>Mean MMSE: 8.8. | Exercise programmes, any length | Usual care or social contact/activities. | Neuropsychiatric symptoms (NPI) | 10/11 |
| Forrester *et al.* (2014) | January 2013 | Dementia diagnosis, any type and severity.<br>Nursing home residents with clinically significant agitation<br>Mean age 78 to 85. | Aromatherapy (using fragrance from plants), any dose, frequency, or fragrance | Placebo aromatherapy | Behavioural symptoms (NPI-total scores) | 9/11 |
| Orgeta *et al.* (2014) | January 2013 | Dementia, any type or MCI<br>Mean age 76–78<br>Mean MMSE 20.9; MMSE ≥20 | Psychological treatment | Usual care | Neuropsychiatric symptoms (NPI, NPI-Q) | 9/11 |
| Ueda *et al.* (2013) | February 2011 | Dementia diagnosis, any type<br>Mean age 75–86.<br>Severity mild to severe. | Music therapy | Usual care | Behaviour (change, BSAD scale, NPI, NPI-Q, CMAI, ESEP) | 7/11 |

*Dyer SM et al. Int Psychogeriatr. November 2017:1-15.*

# NON-PHARM NPS REVIEWS

**Table 1.** Continued

| REVIEW | DATE OF SEARCH | POPULATION CRITERIA, AGE & DEMENTIA SEVERITY OF INCLUDED STUDIES. | INTERVENTION | COMPARISON | OUTCOMES (MEASUREMENT SCALES USED) | QUALITY APPRAISAL (AMSTAR) |
|---|---|---|---|---|---|---|
| Van't Leven *et al.* (2013) | January 2012 | Community-dwelling people with dementia and their caregivers.<br>Age not reported.<br>Mean MMSE 11.0–20.6. | Dyadic psychosocial interventions | Usual care | Behavioural problems (Unclear) | 5/11 |
| Woods *et al.* (2012) | December 2011 | Dementia diagnosis, any sub-type and severity.<br>Mean age 76–853.<br>MMSE range 18–25, mean 20 and moderate to severe impairment. | Cognitive stimulation aimed at general enhancement of cognitive and social functioning. | No treatment, standard treatment or placebo. | Behaviour, problem (change in BPRS, MOSES, NPI) | 10/11 |
| Woods *et al.* (2005) | May 2004 | Dementia of any type or cognitive impairment<br>Mean age 76.3–85.7<br>dementia or moderate to severe cognitive functioning | Reminiscence therapy. Minimum 4 weeks, 6 sessions, led by professional staff or trained care-workers | Control activity or no treatment | Behaviour post-treatment (change in CAPE, PBRS, MDS-ADL) | 9/11 |

*Dyer SM et al. Int Psychogeriatr. November 2017:1-15.*

# AROMATHERAPY

Lavender, lemon balm, melissa oil

Systematic analysis aromatherapy

- Only 2 Studies
- Ballard et al. 2002 – 71 participants
  - Found sig reduction in BPSD
- Burns et al. 2011 – 63 participants
  - Found no sig difference

Conclusion: Insufficient evidence


*Forrester et al. 2014, Ballard et al. 2002, Burns et al. 2011*

# DYADIC CAREGIVER INTERVENTIONS

- Van't Leven et al 2013
  - People with dementia living in the community
  - 6 (806 participants) of 8 studies (1015 participants) had

    No improvement in NPS

*Van't Leven et al. 2013*

# REMINISCENCE THERAPY

- Tap into long term memory to confirm personal identity and bolster self-esteem
- Express key events and experiences like family relationships, schooling & past work
- Mixed Results:
  - Low quality of evidence
  - 20 participants – global improvement in NPS
  - 66 participants – No improvement

*Woods et al. 2005*

# MUSIC THERAPY
# ALIVE INSIDE

**Michael Rossato-Bennett**
**Writer, Director & Producer**

# MUSIC THERAPY

Music matched to patient's preference

- Meta-analysis of 20 studies
- Moderate effects on anxiety
- Small effects on behavioral symptoms
- For studies > 3 mo, music therapy had large effects on anxiety

*Ueda et al. 2013*

# EXERCISE AND PHYSICAL ACTIVITY

- Cochrane Review 2015
- RCTs for older persons with dementia exercise intervention w/ controls
- 17 trials (1067 participants)
- Data not available on 4 of 17
- High heterogeneity
- Quality of evidence: very low

*Forbes et al. 2015*

# EXERCISE AND PHYSICAL ACTIVITY

- 6 trials: improvement in ADLs
- No clear evidence of benefit on NPS
- No effect on depression

*Forbes et al. 2015*

# FUNCTIONAL ANALYSIS

Behavioral Intervention

- Explores meaning or purpose of behavior
- Extends ABC approach
- Hypothesis driven strategies to help family and staff to reduce patient distress and behaviors

*Cook et al. 2012*

# FUNCTIONAL ANALYSIS

RCTs only

18 trials, 14 FA was only one aspect of intervention

Difficult to assess – poorly defined protocols

Could not estimate true FA effect

Improvements in frequency of behaviors (not incidence or severity)

*Cook et al. 2012*

# PSYCHOLOGICAL INTERVENTIONS

Cochrane review

Interventions for anxiety and depression (CBT, therapy, multimodal interventions)

6 RCTs with 439 participants

5 of 6 were of high risk of bias

Sig improvement for depression

Sig improvement clinician rated anxiety (not self rated or CG rated)

*Orgeta et al. 2012*

# COGNITIVE STIMULATION

- 15 RCTs with 7
- Note – review question was to assess cog stimulation effects on cognitive outcomes for people with dementia
- No differences in mood, behavioral function, and problem behaviors

*Woods et al. 2012*

# PHARM NPS REVIEWS

**Table 1.** Continued

| REVIEW | DATE OF SEARCH | POPULATION CRITERIA, AGE & DEMENTIA SEVERITY OF INCLUDED STUDIES. | INTERVENTION | COMPARISON | OUTCOMES (MEASUREMENT SCALES USED) | QUALITY APPRAISAL (AMSTAR) |
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| *Pharmacological interventions* | | | | | | |
| Jansen *et al.* (2011) | June 2009 | Dementia of any severity or type<br>Mean age: 77–88<br>MMSE: moderate | Melatonin, orally administered, for managing cognitive, behavioural (excluding sleep) and mood disturbances. | Placebo or no treatment | Psychopathological behaviors (change in NPI, ADAS-non cog, NPI-Q, at 4–7 weeks) | 9/11 |
| Ma *et al.* (2014) | June 2013 | Dementia of any type<br>Mean age 77–83.<br>Severity not reported[a] | Second generation antipsychotics | Placebo | NPI (change from baseline) | 9/11 |
| Nelson and Devanand (2011) | May 2010 | Diagnosis of dementia and depression.<br>Mean age: 768<br>Mean HDRS: 23<br>Dementia severity not reported | Antidepressants for dementia and depression[b] | Placebo | NPI (response rates) | 7/11 |

*Dyer SM et al. Int Psychogeriatr. November 2017:1-15.*

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| Pieper *et al.* (2013) | March 2012 | Dementia diagnosis, any type.<br>Mean age: intervention arm: 85, control arm 87.<br>Severity: moderate to severe. | Interventions targeting a reduction in the person's pain or distress and/or behaviour. Includes pain medication, analgesia, and drug therapy. | Usual care | Behaviour (NPI-NH total at endpoint)[c] | 7/11 |
| Seitz *et al.* (2011) | October 2011 | Dementia of any type or severity, without concomitant major depressive disorder<br>Mean age: NR<br>MMSE: 8–23. | Antidepressants with primary outcome treatment of psychosis, agitation or other NPS. | Placebo | Behaviour (NPI change in total score) | 11/11 |
| Seitz *et al.* (2013) | February 2011 | Dementia of any type, >50% in residential care.<br>Mean age: 84–85<br>Mean MMSE: 7–11 | Mood stabilizers (anticonvulsants)[d] | Placebo | Neuropsychiatric symptoms (change in BPRS total score) | 7/11 |
| Tan *et al.* (2014) | November 2013 | Probable or possible Alzheimer's disease.<br>Mean age 73–86<br>MMSE range: 10–19 | Cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and memantine | Placebo | Behaviour (change in NPI scale) | 7/11 |

*Dyer SM et al. Int Psychogeriatr. November 2017:1-15.*

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*Dyer SM et al. Int Psychogeriatr. November 2017:1-15.*

# PHARMACOLOGIC INTERVENTIONS

- 4 of 7 reviews of pharm interventions show sig improvement in NPS
- 2 cholinesterase inhibitors reviews showed benefit
  - 10mg donepezil
  - 24mg galantamine
- Pain Management (sig improve)
- Atypical Antipsychotics (sig improve)

*Dyer SM et al. Int Psychogeriatr. November 2017:1-15.*

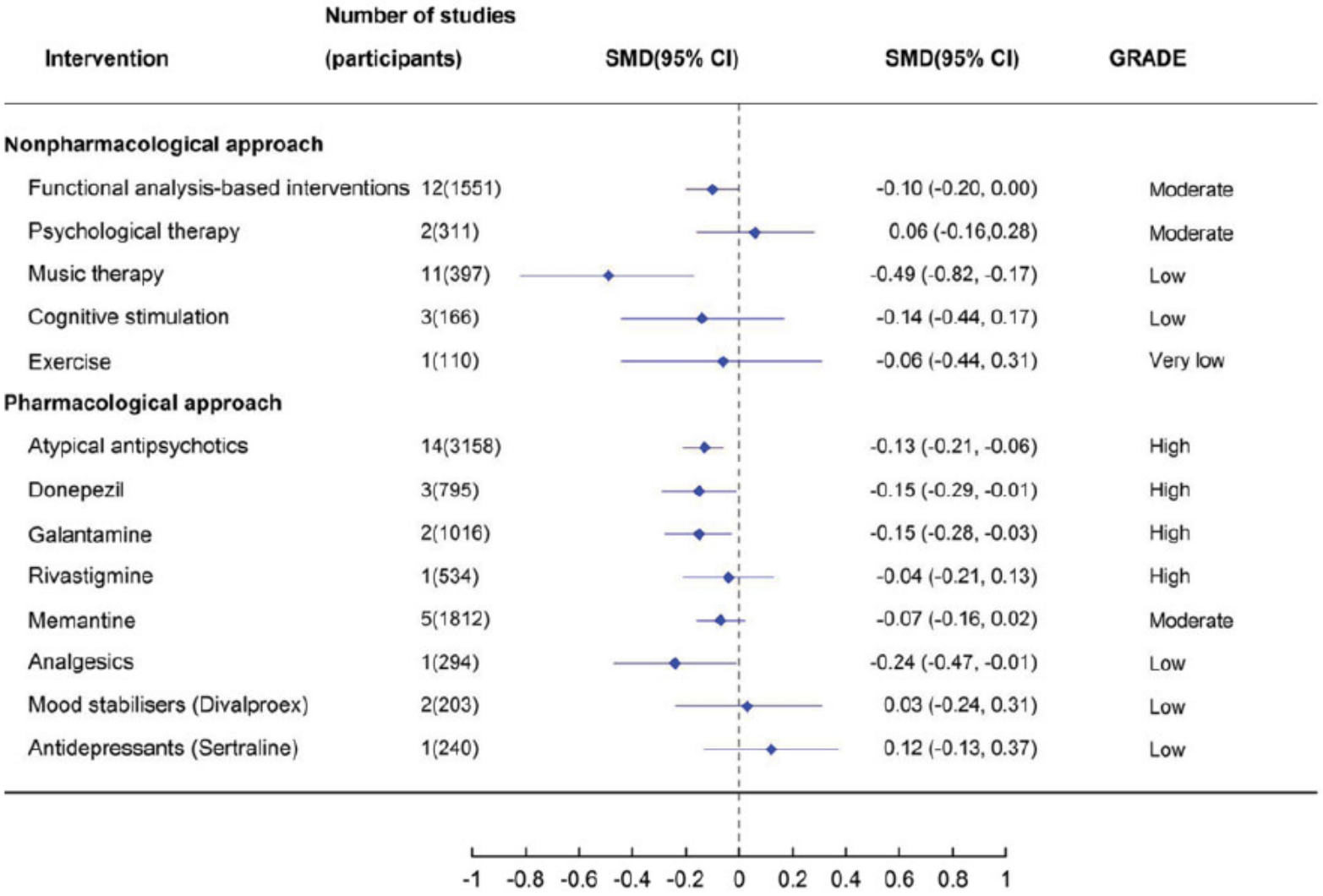


**Figure 2.** (Colour online) The effect of alternative treatments for the management of behavioural and psychological symptoms of dementia on global BPSD measures. Note: antidepressant estimate of effect is from a review of antidepressants for the treatment of agitation and psychosis. Abbreviations: CI = confidence interval; SMD = standardized mean difference.

# ADVERSE REACTIONS

| | |
|---|---|
| *Pharmacological interventions* | |
| Atypical antipsychotics (Ma, 2014) | Significantly higher risk for somnolence, extrapyramidal symptoms, cerebrovascular adverse events, urinary tract infections, edema, gait abnormality, and death compared to placebo. Some adverse effects had incidence rates of >5% and were observed in most trials. |
| Cholinesterase inhibitors (Tan, 2014) | Dropouts from the trials for any reason were significantly greater for 12 mg daily rivastigmine and 32 mg daily galantamine than with placebo. Dropouts due to adverse events were significantly higher for 10 mg daily donepezil, 12 mg daily rivastigmine, and 32 mg daily galantamine compared to placebo.<br>The review states "Significant risks were reported for the following adverse events: dizziness and headache on 5 mg daily donepezil; nausea, vomiting, diarrhea, and anorexia on 10 mg daily donepezil; nausea, vomiting, diarrhea, anorexia, and dizziness on galantamine; and nausea, vomiting, diarrhea, anorexia, dizziness, and headache on rivastigmine." |
| Memantine (Tan, 2014) | Memantine was not significantly associated with more dropouts or adverse events. |
| Analgesics (Pieper, 2013) | Only one RCT which had very few reported adverse events (three participants were excluded because of drowsiness and nausea) and similar loss to follow-up in intervention and control group. |
| Mood stabilizers (Divalproex) (Seitz, 2013) | Similar or lower rates of withdrawals overall and withdrawals due to adverse events with divalproex compared to placebo in the two RCTs. |
| Melatonin (Jansen, 2011) | The review states "No reported adverse effects." However, the authors did state a significant worsening of mood after 12 months. |
| Antidepressants (Sertraline) (Seitz, 2011) | Only one RCT, no difference in withdrawal due to adverse events or withdrawal due to any causes in sertraline treated group compared to placebo. |

# SSRIS

- Cochrane Database, 9 studies
  - In 2 studies citalopram and sertraline showed improvement in agitation


*Seitz, D.P., et al., Antidepressants for agitation and psychosis in dementia. Cochrane Database Syst Rev, 2011(2).*

# MOOD STABILIZERS AND ANTICONVULSANTS

## Carbamazepine

- 1 meta-analysis & 3 RCTs **support** use in treating BPSD
- Especially aggression & hostility

## Valproate/Valproic Acid

- 1 meta-analysis & 5 RCTs **did not** support use in treating BPSD
- Suggestion of association with **increased mortality** in patients with dementia

*Yeh, Y.C. and W.C. Ouyang, Mood stabilizers for the treatment of behavioral and psychological symptoms of dementia: an update review. Kaohsiung J Med Sci, 2012. 28(4): p. 185-93.*

# MOOD STABILIZERS AND ANTICONVULSANTS

## Oxcarbamazepine

- 1 RCT **did not** support use in BPSD

## Gabapentin, Topiramate, Lamotrigine

- **Supportive** case series
- Several reports of patients with lewy body dementia worsening with gabapentin.

## Lithium

- Few studies, **little to no benefit** in BPSD

*Yeh, Y.C. and W.C. Ouyang, Mood stabilizers for the treatment of behavioral and psychological symptoms of dementia: an update review. Kaohsiung J Med Sci, 2012. 28(4): p. 185-93.*

# FDA PUBLIC HEALTH ADVISORY: DEATHS WITH ANTIPSYCHOTICS IN ELDERLY PATIENTS WITH BEHAVIORAL DISTURBANCES

In 15 of 17 placebo controlled trials (n=5106) performed with olanzapine, aripiprazole, risperidone, or quetiapine in older demented patients with behavioral disorders receiving the active drug had higher mortality rates.

Average trial time was 10 weeks.

U.S. Food and Drug Administration, U.S. Department of Health and Human Services. Public Health Advisory: Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances. (http://tinyurl.com/6ws7ap2)
Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA . 2005;294(15):1934-43.

# FDA PUBLIC HEALTH ADVISORY: DEATHS WITH ANTIPSYCHOTICS IN ELDERLY PATIENTS WITH BEHAVIORAL DISTURBANCES 2003

**There was an approximate 1.6-1.7 fold increase in mortality in these studies.**

The rate of death was about **4.5% in drug-treated** patients and about **2.6% in the placebo group.**

Examination of the specific causes of these deaths revealed that most were either due to **heart related events (e.g., heart failure, sudden death) or infections (mostly pneumonia).**

*U.S. Food and Drug Administration, U.S. Department of Health and Human Services. Public Health Advisory: Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances. (http://tinyurl.com/6ws7ap2)*

*Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA . 2005;294(15):1934-43.*

# MORTALITY RISK - SCHNEIDER ET AL. (2005)

- Retrospective meta-analysis of 15 placebo-controlled trials (9 unpublished) of AP use in dementia patients
- § 3353 antipsychotic, 1757 placebo, for 10-12 weeks
- 16 permutations of AP (3 aripiprazole, 5 olanzapine, 3 quetiapine, 5 risperidone),4 outpatient and 11 nursing home
- 8 dose adjustment, 2 fixed, 5 ranged
- 3.5% (118 deaths) SGA mortality, vs 2.3% (40) placebo
- OR = 1.54, p=0.02
- RR = 1.65
- Risk difference 0.01 (p=0.01)

# 2008 BLACK BOX WARNING EXPANDED TO ALL ANTIPSYCHOTICS

- Based on two 2007 retrospective, nonrandomized observational epidemiologic studies from Canada: elderly mortality rates on FGA =/> SGA
- Schneeweiss et al (2007)
  - Population-based cohort study, 37,241 people 65+yo in B.C.
  - 1/3 (12,882) FGA vs. 2/3 (24,359) SGA (Risp >> Quet, Olan, Cloz)
  - Primary outcome: mortality @180 days
  - Mortality hazard ratio 1.47 for FGA: SGA within 180 days of tx initiation
  - 32% greater, dose-dependent risk of death
  - 14.1% (1822) FGA deaths, 9.6% (2337) SGA deaths

# 2008 BLACK BOX WARNING EXPANDED TO ALL ANTIPSYCHOTICS (CONT...)

- Gill, S et al (2007)
  - Retrospective cohort study based on public health databases
  - 27,259 pairs of 66+yo in Ontario, Can
  - 3 cohorts FGA, SGA, and no AP
  - Matched by demographic (community vs long-term care) and clinical status
  - New SGA sig higher mortality rate vs no drug 30-180 days after initiation:
  - Hazard Ratio: 1.31 community, 1.55 LTC
  - Mortality risk higher for FGA vs SGA

*Gill, S et al (2007) Ann Intern Med. 146:775-586*

# WHO WOULD BENEFIT MOST?

- 15 RCTs and SGAs for agitation and psychosis of dementia (87% AD)
- 3 aripiprazole, 4 olanzapine, 4 risperidone, 3 quetiapine, 1 olanzapine vs risperidone
- 11 nursing home, 4 community
- Age 81yo (mean), 70% female
- Psychosis scores improved on risperidone only
- Global neuropsych improved with aripiprazole and risperidone
- Better response in:
  - Dementia without psychosis (i.e. agitation alone)
  - More severe CI
  - Nursing home status
- NNT = 5 to 14

Schneider LS et al. (2006a). *Am J Geriatr Psychiatry*. 14(3):191-210.

# ARE THEY EFFECTIVE: CATIE-AD TRIAL

- **C**linical **A**ntipsychotic **T**rials of **I**ntervention **E**ffectiveness–**A**lzheimer's **D**isease
- NIMH-funded, study SGA effectiveness
- Double blind placebo-controlled, 42 outpatient U.S. sites, 9 months
- N=421 AD with delusions, hallucinations, agitation, or aggression
- Avg 78yo, 56% female
- Results: Risperidone, olanzapine, quetiapine = placebo
- Primary outcome: time to discontinuation, up to 36wk
- Secondary outcome: CGI score, 12 weeks
- Limitations: May have underdosed, low event rates, generalizability

*Schneider LS, et al. (2006b). N Engl J Med. 355(15):1525-38*

# CHANGES FOLLOWING THE BLACK BOX WARNINGS

- Similar prescribing for patients with dementia, but now nursing homes with informed consent policies for antipsychotics (Lester et al., 2011)
- Minimal impact of antipsychotic use in noninstitutionalized patients with dementia (Singh and Nayak, 2016)
- Decreased AP use in patients with MDD (~20%) (Rhee et al., 2018)
- Increase in non-antipsychotic psychotropics (benzos, antidementia)
- Cumulative doses w/ increased mortality rate (Neilsen et al, 2016)
  - Retrospective cohort study of 45,894 patients with AD
  - 0-90 daily defined dosage (DDD) (HR 2.20, $p<0.001$)
  - 90-365 DDD (HR 1.81, $p<0.001$)
  - 365-730 DDD (HR 1.06, $p=0.322$)

# NUMBER NEEDED TO HARM

## MAUST ET AL 2015

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) |

Abbreviation: NA, not applicable; NNH, number needed to harm.

*Maust et al. JAMA Psychiatry. 2015 May 1; 72(5): 438–445*

# IN SUMMARY

- Full Assessment
- Try non-pharmacologic interventions first
- Medications only for mod to severe NPS
- Clearly identify target symptoms
- Time limited use of medication

Thank you

Questions

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