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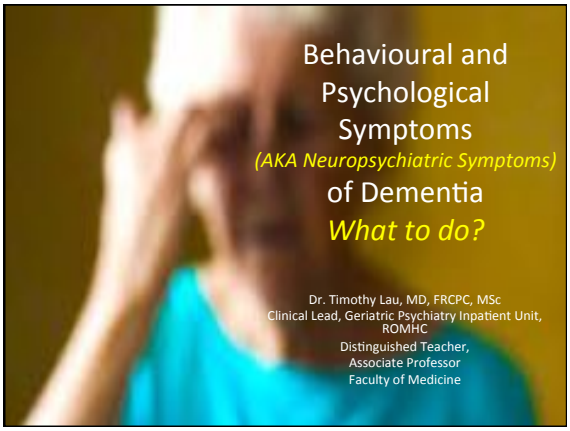
RGPEO
Regional Geriatric Program of Eastern Ontario

BPSD What to do?

Geriatric Refresher Day
11:30-12:30, Wed March 4th, 2015
St Elias Centre, Ottawa Ontario



Behavioural and Psychological Symptoms *(AKA Neuropsychiatric Symptoms)* of Dementia *What to do?*

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Distinguished Teacher,
Associate Professor
Faculty of Medicine

Pre-Test 1

- Which of the following BPSD symptoms respond to medications
  - a) Wandering, exit seeking
  - b) Verbal aggression
  - c) Anxiety
  - d) Annoying activities (touching, hugging…)
  - e) Hoarding or "Stealing"
  - f) Inappropriate undressing and dressing

Pre-Test 2

- Behavioural and Psychological Symptoms of Dementia (BPSD) are best treated with
  - a) Non-pharmacological interventions
  - b) Benzodiazepines
  - c) Antidepressants
  - d) Antipsychotics
  - e) Both medications and environmental interventions

Pre-Test 3

- Which of the following is **<u>are correct</u>** regarding atypical antipsychotics and dementia
  - a) There is an increased risk of death in placebo controlled short term studies
  - b) There is an increased risk of death in placebo controlled long term studies
  - c) They are the most effective medications to treat severe aggression
  - d) They are preferable to physical restraints

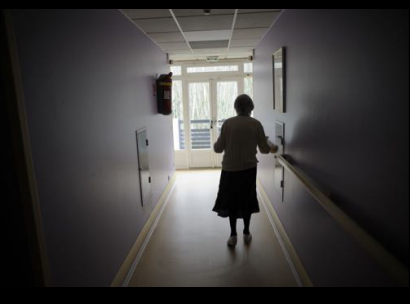
Objectives

1. Review common behavioural and psychological problems seen in patients affected by dementia
2. Review the evidence for treatment
3. Discuss some cases

Overview

1. Introduction
   - *What is BPSD (NPS)?*
   - *What causes it?*
   - *Why is it important?*
2. How do we access BPSD?
3. How do we treat it?
4. Cases

What is BPSD?



BPSD

- Dramatic presentations
  - Cognitive deficits are the clinical hallmark of dementia but noncognitive symptoms are common and can dominate disease presentation.
  - Are not equivalent to acute onset

What is BPSD?

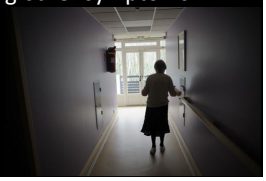
Behavioral symptoms
Usually identified on the basis of observation of the patient, including physical aggression, screaming, restlessness, agitation, wandering, culturally inappropriate behaviors, sexual disinhibition, hoarding, cursing and shadowing.

Psychological symptoms
Usually and mainly assessed on the basis of interviews with patients and relatives; these symptoms include anxiety, depressive mood, hallucinations and delusions. A psychosis of Alzheimer's disease has been accepted since the 1999 conference.

A consensus group, consisting of some 60 experts in the field, from 16 countries, produced a statement on the definition of the BPSD:
"Symptoms of disturbed perception, thought content, mood or behavior that frequently occur in patients with dementia".

BPSD

- What is BPSD?
  - An array of neuropsychiatric symptoms, such as agitation, aggression, delusions, hallucinations, repetitive vocalizations, and wandering, among other symptoms.



What causes BPSD?

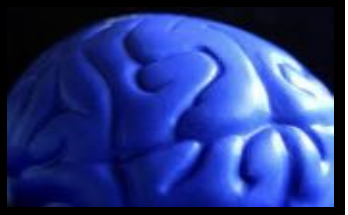


Table 3. Pathogenic mechanisms of catastrophic reactions. Reprinted with permission from Haupt, 1996.

Organic variables
Brain damage (corpora amygdala, temporal lobes, hypothalamus)
Neurotransmitter dysfunction (decreased serotonin levels in the brain)
Psychological variables
Encountering a new environment
Realization that one is forgetful or ill
Reduced ability to communicate
Acting out psychotic distress
Accentuation of premorbid personality traits
Problematic relationship to caregiver in the past (troubled dyad)
Environmental variables
Unidentified noise
Inadequate lighting
Moving to unfamiliar places
Adversarial patient management style

Individual factors

- Pain
- Constipation or fecal impaction
- Infections
- Injury
- Dehydration
- Nutritional problems
- Delirium
- Psychosis
- Depression
- Anxiety disorders
- Sleep disorders
- Substance or medication abuse or withdrawal
- Hearing and vision problems
- Worsening of chronic medical conditions
- Recent onset of new medical condition
- Medications that have the potential to alter cognition or mood

Social and Environmental Factors

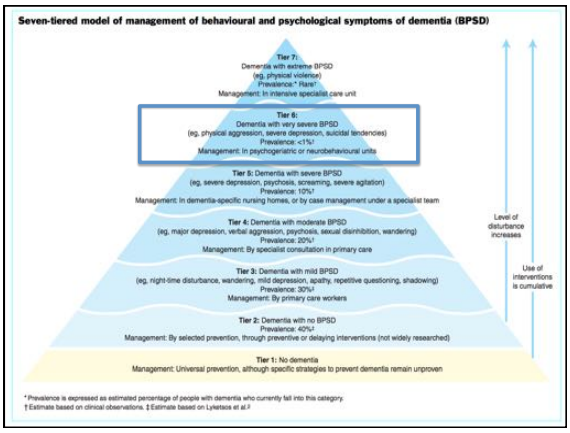
- Changes in social or family situation
- New stressors or situational factors such as changes in staff
- Lack of social activities
- Lack of meaningful activities
- Lack of positive (reinforcing) experiences
- Deviations from normal life patterns, preferences, and autonomy
- Change in room (i.e., relocation)

What is in the DDx?

- Delirium
- Depression/anxiety/mania
- "Check the pee and the poop"
  - Pain/constipation/UTI

BPSD

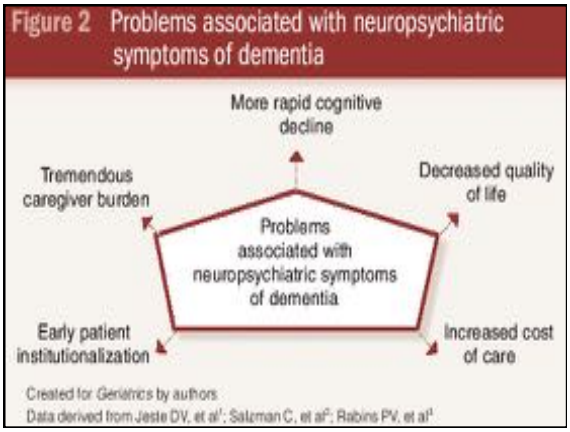
- How common?
  - Neuropsychiatric symptoms have been observed in 60% to 98% of patients with dementia, especially in later stages.



Why is it important?

Why is it important?

1. BPSD is common in dementia
2. BPSD is associated with significant suffering for both the patient and family, is associated with functional decline, institutionalization and death
3. Compared to the other symptoms of dementia they are more treatable.
4. Treatment offers the best chance to reduce family burden and lower societal costs.



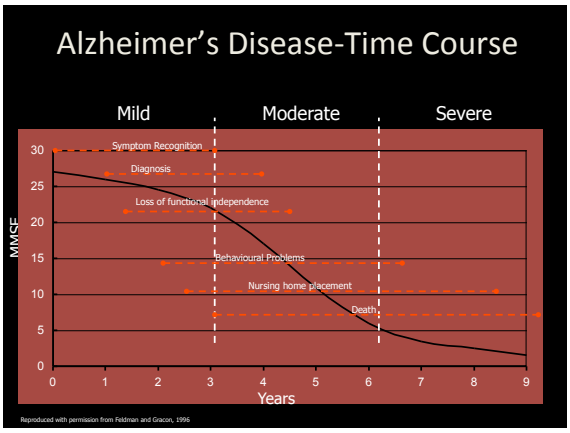
Management of Dementia

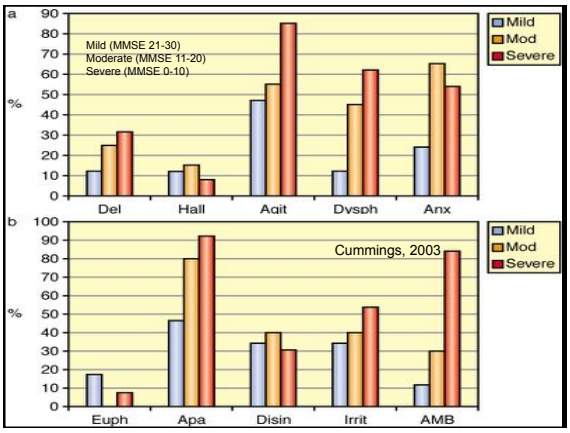
- 5 Key Symptom Areas
  1. **ADL's**
  2. **Behaviour** and personality (BPSD)
  3. Cognition
  4. Depression
  5. Effect on others

Incidence 90% Tariot 1999
Prevalence 60-90% Lyketsos 2002
NSG home 70-90% Ballard 2001
Community 60% Lysketsos 2000

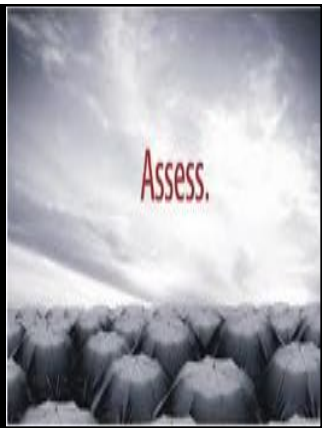
Symptoms varies by type and …

- AD: apathy, agitation/aggression, anxiety
- VaD: depression, agitation/aggression, apathy
- LBD: apathy, delusions/visual hall, sleep disorders
- FTD: apathy, agitation/aggression, disinhibition





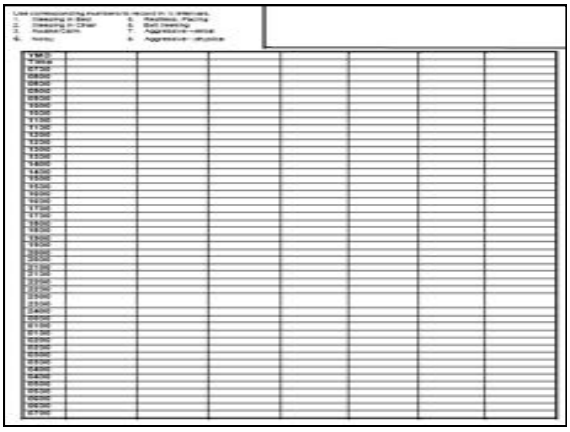
How do we…



Assessement: the ABC's

- A: ANTECENDENTS
  - under, overstimulation, hunger, fear, pain
- B: BEHAVIOURS
  - Resistance to care, wandering, calling out
- C: CONSEQUENCES
  - Attention, food, care (re-enforced)

- Scales to measure the nature, severity, and frequency and the DOS to determine patterns and the ABCs



1986
The Cohen-Mansfield Agitation Inventory (CMAI) focused specifically on behaviors such as hitting, pacing and screaming (Cohen-Mansfield et al., 1989; Cohen-Mansfield, 1996).

1987
The Behavioral Pathologic Rating Scale for Alzheimer's disease (BEHAVE-AD) focused on specific symptoms in AD, different from those seen in other neuropsychiatric disorders, such as delusion that people are stealing things, fear of being left alone and fragmented sleep. (Reisberg et al., 1996).

1994
The Neuropsychiatric Inventory (NPI) has frequency and severity scales for behaviors common to AD, but also includes scales for other dementias (Cummings et al., 1994).

1995
The Consortium to Establish a Registry in AD (CERAD) Behavioral Scale focused on both behavioral and psychological symptoms (Tariot et al., 1995; Tariot, 1996).

Box. Neuropsychiatric Symptom Rating Scales

Agitated Behavior Inventory for Dementia (ABID)
Agitation-Calmness Evaluation Scale (ACES)
Alzheimer Disease Assessment Scale, noncognitive portion (ADAS-noncog)
Bech-Rafaelsen Mania Scale (BRMS)
Behavior Observation Scale for Institutional Psychogeriatric Patients (OIP)
Behavior Rating Scale for Dementia (by the Consortium to Establish a Registry for Dementia) (BRSD)
Behavioral Pathology in Alzheimer Disease Rating Scale (BEHAVE-AD)
Brief Psychiatric Rating Scale (BPRS)
Caregiver Burden Questionnaire (CBQ)
Clinical Global Impression of Change (1=very much improved to 7=very much worse) (CGIC)
Clinical Global Impression Scale (CGIS)
Clinicians Interview Based Impression of Change plus caregiver input (CIBIC-plus)
Cohen-Mansfield Agitation Inventory (CMAI)
Hamilton Rating Scale for Depression (Ham-D)
Iowa Caregiver Stress Inventory (CSI)
Neurobehavioral Rating Scale (0=not present to 7=extremely severe), derived from the Brief Psychiatric Rating Scale (NRS)
Neuropsychiatric Inventory (usually 10 items, 120 points) (NPI)
Neuropsychiatric Inventory-Nursing Home version (12 items, 144 points) (NPI-NH)
Neuropsychiatric Inventory minus 5 "mood" items (NPI-NM)
Overt Aggression Scale (OAS)
Positive and Negative Syndrome Scale-Excited Component (PANSS-EC)
Revised Memory and Behavior Problem Checklist (RMBPC)
Screen for Caregiver Burden (SCB)
Social Dysfunction and Aggression Scale (SDAS-9)

Assessment

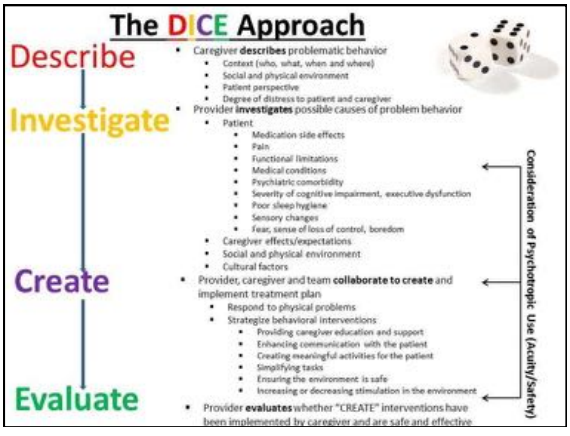
- Comprehensive assessment to rule out
  - pain (Cohen-Mansfield and Mintzer, 2005; Sink *et al.*, 2005),
  - delirium (Sink *et al.*, 2005), and
  - environmental or interpersonal factors (Sink *et al.*, 2005) which may precipitate behaviors.
- Non-pharmacological interventions are usually recommended as first-line treatments for BPSD.

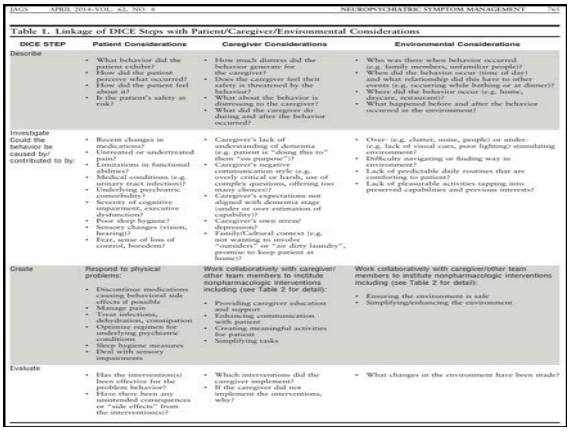
Assessment

- Unfortunately,
  - knowledge of psychosocial interventions in LTC is low (Cohen-Mansfield and Jensen, 2008),
  - access to services for these interventions is limited (Conn, 1992; Burns *et al.*, 1993; Meeks, 1996; Reichman *et al.*, 1998; Seitz *et al.*, 2011),
  - their effectiveness may be modest (Seitz *et al.*, 2012), and
  - patients may not cooperate with these interventions (Cohen-Mansfield *et al.*, 2012).

Assessment and Management

1. Safety should be the first concern
   - In urgent situations, or when symptoms are severe:
     - It is appropriate to initiate pharmacological and nonpharmacological interventions together
2. Reducing patient and caregiver's vulnerability and exposure to stressors
   - Addressing a patient's BPSD
   - Supporting Caregiver's psychological morbidities
3. Increasing Caregiver's Resources
   - Training
   - Education
   - Social supports
   - In LTC, more staff, HIN in Ontario





JAGS APRIL 2014-VOL. 62, NO. 4 NEUROPSYCHIATRIC SYMPTOM MANAGEMENT 765

Table 1. Linkage of DICE Steps with Patient/Caregiver/Environmental Considerations

DICE STEP	Patient Considerations	Caregiver Considerations	Environmental Considerations
Describe	• What behavior did the patient exhibit? • Has the patient perceived who occurred? • How did the patient feel about it? • Is the patient's safety at risk?	• How much distress did the behavior generate for the caregiver? • Has the caregiver feel their safety is threatened by the behavior? • What about the behavior is distressing to the caregiver? • What did the caregiver do during and after the behavior occurred?	• Who was there when behavior occurred (e.g. family members, unfamiliar people)? • When did the behavior occur (time of day) and what was occurring? Were other events (e.g. occurring while bathing or at dinner)? • Where did the behavior occur (e.g. home, daycare, restaurant)? • What happened before and after the behavior occurred in the environment?
Investigate Could the behavior be caused by/ contributed to by:	• Recent changes in medications? • Untreated or undertreated pain? • Limitations in functional abilities? • Medical conditions (e.g. urinary tract infection)? • Underlying psychiatric comorbidity? • Severity of cognitive impairment, executive dysfunction? • Poor sleep hygiene? • Sensory changes (vision, hearing)? • Fear, sense of loss of control, boredom?	• Caregiver's lack of understanding of dementia (e.g. patient is "doing this to" them "on purpose")? • Caregiver's negative communication style (e.g. talking too fast, hands, use of complex questions, offering too many choices)? • Caregiver's expectations not aligned with dementia stage (under or over estimation of capability)? • Caregiver's own stress/ depression? • Caregiver's cultural context (e.g. not wanting to involve "outsiders" or "air dirty laundry", promise to keep patient at home)?	• Over- (e.g. clutter, noise, people) or under- (e.g. lack of visual cues, poor lighting) stimulating environment? • Difficulty navigating or finding way in environment? • Lack of predictable daily routines that are meaningful to patient? • Lack of pleasurable activities tapping into preserved capabilities and previous interests?
Create	Respond to physical problems: • Discontinue medications causing behavioral side effects if possible • Manage pain • Treat infections, dehydration, constipation • Optimize regimen for underlying psychiatric conditions • Sensory aid measures • Deal with sensory impairments	Work collaboratively with caregiver/ other team members to institute nonpharmacologic interventions including (see Table 2 for detail): • Providing caregiver education and support • Enhancing communication with patient • Creating meaningful activities for patient • Simplifying tasks	Work collaboratively with caregiver/other team members to institute nonpharmacologic interventions including (see Table 2 for detail): • Ensuring the environment is safe • Simplifying/enhancing the environment
Evaluate	• Has the intervention(s) been effective for the patient's behavior? • Have there been any unintended consequences or "side effects" from the intervention(s)?	• Which interventions did the caregiver implement? • If the caregiver did not implement the interventions, why?	• What changes in the environment have been made?

- What behaviours respond to medications?

Behaviours not generally amenable to pharmacotherapy

- Wandering, exit seeking
- Verbal aggression
- Resistance to care
- Annoying activities (touching, hugging…)
- Inappropriate sexual behaviour
- Refusal of food, medications
- Hoarding or "Stealing"
- Inappropriate urination or defecation (including smearing of feces)
- Spitting
- Inappropriate undressing and dressing (layering, hoarding taking other patients clothes)

Behaviours not generally amenable to pharmacotherapy

- Constant requests, repetitions
- Excessive noisiness
- Hiding things
- Pushing wheelchair-bound patients
- Tearing things, flushing things down toilets
- Eating inedible things (including feces)
- Tugging at or removing restraints
- Refusing to leave room
- Physical disruptiveness

Behaviours that may be amenable to pharmacotherapy

- Anxiety: restlessness, hand-wringing, pressured pacing, fidgeting, agitation
- Sadness: crying, anorexia, terminal insomnia, nihilism, guilt
- Withdrawn: apathy, quiet negativity, anorexia, sulleness, uncooperation
- Markedly bizarre or regressed behaviour from previous standards
- Over-elation
- Overly boisterous: verbal hostility, aggressiveness, argumentativeness
- Delusions: ideas of reference, paranoia, persecuted, sensory
- Hallucinations

General Guidelines

- Prescribing must be informed and judicious,
- utilizing low starting doses;
- slow and cautious dose titration, and
- careful monitoring for the emergence of side effects.

General Guidelines

- Before deciding whether to treat BPSD with medication, the following questions must be addressed:
  1. Does the particular symptom or behavior warrant drug treatment, and why?
  2. Which type of medication is most suitable for this symptom or behavior?
  3. What are the predictable and potential side effects of a particular drug treatment?
  4. How long should the treatment be continued?

General Guidelines

- Drug treatment for BPSD should only be initiated after these symptoms have been found to:
  1. have no physical cause
  2. be unrelated to the effects of other medication
  3. not respond to or be appropriate for non-pharmacological interventions.

Should we suggest medications?

Achieve Balance Between Efficacy & Side Effects

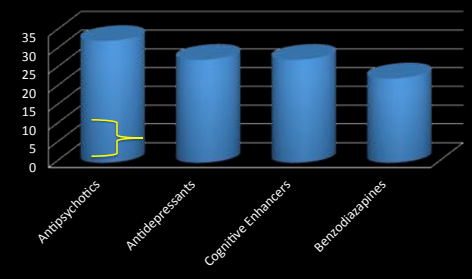
Improvement in symptoms of BPSD:
Aggression
Agitation
Apathy
Depression
Psychosis

Anticholinergic effects
Sedation & Falls
EPS
Diabetes
GI ASE (with ADs)

Efficacy

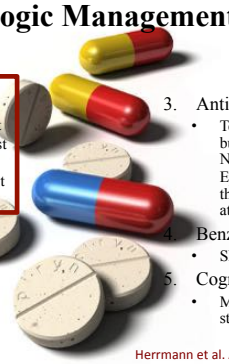
Safety & Tolerability

Percentage usage in LTC



InternationalPsychogeriatrics(2013), Seitz et al. Pharmacological treatment for neuropsychiatric symptoms of dementia in LTC

Pharmacologic Management of BPSD



1. Atypicals
   - Remain the best studied and most effective but side effects limit their use
2. Antidepressants
   - Inconclusive evidence for Trazadone
   - Citalopram: Recent double blind-PC-RCT
   - JAMA 2014
3. Anticonvulsants
   - Tegretol can be effective but poorly tolerated. Negative studies with Epival. Not as thoroughly studied as atypicals
4. Benzodiazepines
   - Short term use only
5. Cognitive enhancers
   - Memantine negative study

Herrmann et al. Alzheimer's Research & Therapy 2013, 5(Suppl 1):S5

Atypicals

- The 15 studies of atypical antipsychotics involved risperidone (N = 6), olanzapine (N = 4), quetiapine (N = 3), and aripiprazole (N = 3).

Herrmann et al. Alzheimer's Research & Therapy 2013, 5(Suppl 1):S5

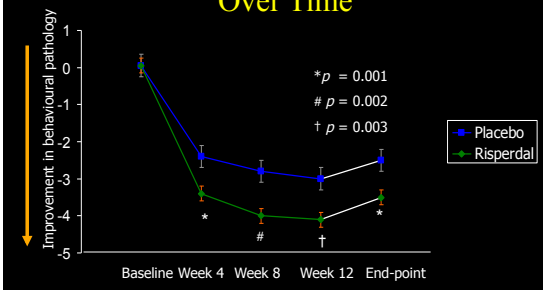
Risperidone

- Available as M-Tabs and Consta depot
- Best studied, best evidence
- High rates of EPS
- Dose range 0.25-2 mg per day.

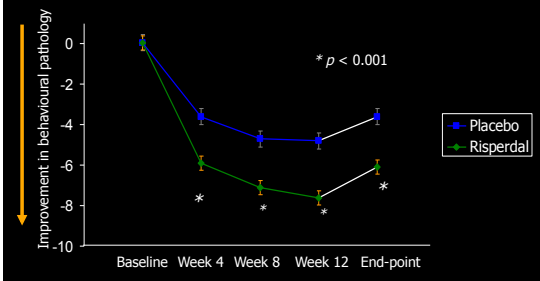
Pooled Analysis of Phase III Trials

- De Deyn, Katz and Brodaty trials
- 1150 elderly subjects (excl. patients on haloperidol)
  - 722 risperidone
  - 428 placebo
- Suitable for pooling:
  - all nursing home/institutionalized
  - same duration (12 weeks)
  - similar dosing ranges (different schedules)

Pooled Analysis: BEHAVE-AD Psychosis Subscore Change Over Time



Pooled Analysis: BEHAVE-AD Score Change Over Time



Atypicals and Severity of Aggression

- Katz IJGP 2007
  - metanalysis of 4 Risperidone Trials

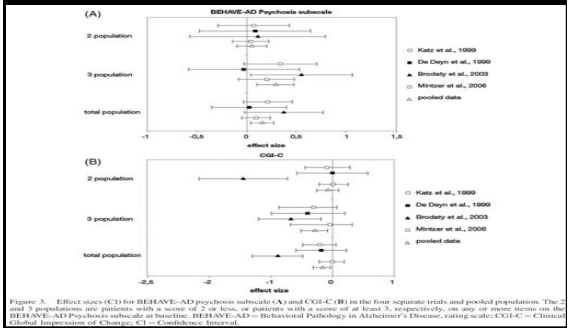


Figure 3. Effect sizes (CI) for BEHAVE-AD psychosis subscale (A) and CGI-C (B) in the four separate trials and pooled population. The 2 and 3 populations are patients with a score of 2 or less, or patients with a score of at least 3, respectively, on any or more items on the BEHAVE-AD Psychosis subscale at baseline. BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease, rating scale; CGI-C = Clinical Global Impression of Change; CI = Confidence Interval.

3 Aripiprazole RCTs

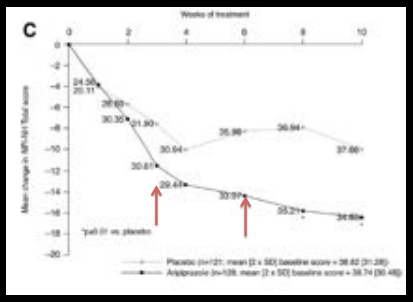
	Location	N	RCT design (10wks)	Population	Outcome
De Deyn 2005	Multicenter, Belgium **(RH)**	N=208	Flexible dose (2-15mg) vs PBO Mean 10mg	55-95 AD (DSM) MMSE 6-24 NPI psychosis ≥5 (x 1 mo)	NPI total (-) Caregiver-Rated BPRS (+) Clinician rated
Streim 2008	35 US centers **(LTC)**	N=256	Flexible dose (2-15mg) vs PBO Mean 9mg		$NPI_{psychosis}$ (-) NPI_{total} (+) CMAI (+)
Mintzer 2007	81 International centers **(LTC)**	N=480	Fixed does 2, 5, 10 mg Vs PBO		NPI_{psych} (+) 10mg NPI_{total} (+) 5-10mg CMAI (+) 5-10mg
4 overlapping authors, employees of BMS / Otsuka. Industry founded					

RH & Home with caregiver Psychosis in AD, n=208 De Deyn *et al* 2005

TABLE 1. Mean Changes in Efficacy Measures From Baseline at Week 10 (LOCF)

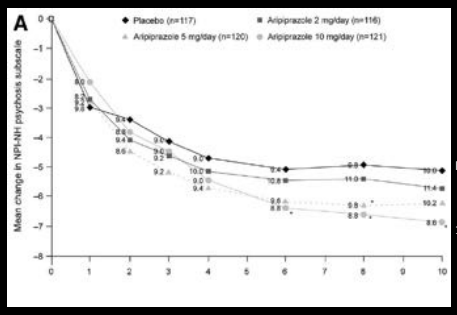
	Placebo			Aripiprazole			
Efficacy Measure	n	Mean Baseline	Mean Change	n	Mean Baseline	Mean Change	*P*
NPI Psychosis*	100	12.12	−5.52	103	12.69	−6.55	0.169
NPI Total*	100	40.08	−9.75	103	39.82	−11.20	0.582
BPRS Psychosis†	93	5.25	−1.27	99	5.46	−1.93	0.029
BPRS Core†	97	11.68	−2.7	101	12.28	−3.9	0.042
BPRS Total†	95	43.42	−6.58	100	43.63	−8.53	0.153
CGI-S‖	100	4.84	−0.54	102	4.83	−0.69	0.345
CGI-I‖	100	—	3.07	103	—	3.17	0.564
MMSE‖	86	14.13	0.53	94	14.35	−0.81	0.001

LTC, Psychosis in AD n=256
Streim *et al* 2008



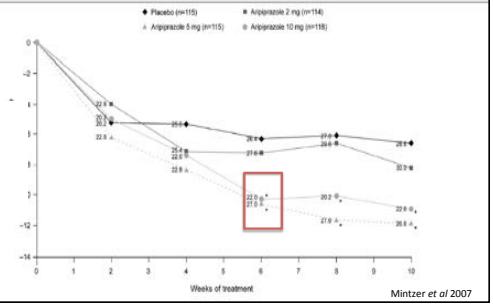
Streim *et al* 2008

LTC, Psychosis in AD, n=480
Mintzer *et al* 2007



LTC, Psychosis in AD n=480

FIGURE 5. Mean Change from Baseline in CMAI Score (LOCF; 2 × Standard Deviation Values Are Shown in Brackets at Each Data Point)



Mintzer *et al* 2007

Article

Clinical Symptom Responses to Atypical Antipsychotic Medications in Alzheimer's Disease: Phase 1 Outcomes From the CATIE-AD Effectiveness Trial

David L. Sultzer, M.D.
Sonia M. Davis, Dr.P.H.
Pierre N. Tariot, M.D.
Karen S. Dagerman, M.S.
Barry D. Lebowitz, Ph.D.
Constantine G. Lyketsos, M.D., M.H.S.
Robert A. Rosenheck, M.D.
John K. Hsiao, M.D.
Jeffrey A. Lieberman, M.D.
Lon S. Schneider, M.D.
CATIE-AD Study Group

Objective: The study measured the effects of atypical antipsychotics on psychiatric and behavioral symptoms in patients with Alzheimer's disease and psychosis or agitated behavior.

Method: The Clinical Antipsychotic Trials of Intervention Effectiveness—Alzheimer's Disease (CATIE-AD) Alzheimer's disease effectiveness study included 421 outpatients with Alzheimer's disease and psychosis or agitated/aggressive behavior. Patients were assigned randomly to masked, flexible-dose treatment with olanzapine, quetiapine, risperidone, or placebo for up to 36 weeks. Patients could be randomly reassigned to a different medication at the clinician's discretion, which ended phase 1. Psychiatric and behavioral symptoms, functioning, cognition, care needs, and quality of life were measured at regular intervals.

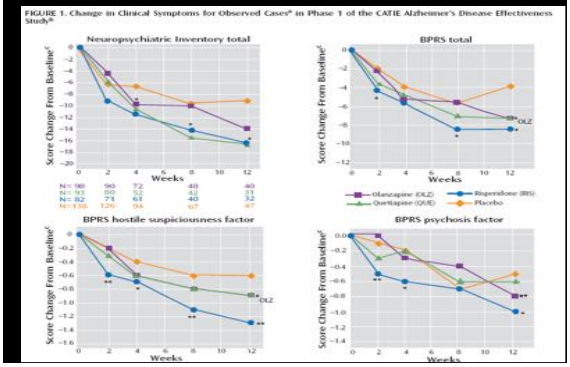
Results: In relation to placebo, the last observation in phase 1 showed greater improvement with olanzapine or risperidone on the Neuropsychiatric Inventory total score, risperidone on the Clinical Global Impression of Changes, olanzapine and risperidone on the Brief Psychiatric Rating Scale (BPRS) hostile suspiciousness factor, and risperidone on the BPRS psychosis factor. There was worsening with olanzapine on the BPRS withdrawn depression factor. Among patients continuing phase 1 treatment at 12 weeks, there were no significant differences between antipsychotics and placebo on cognition, functioning, care needs, or quality of life, except for worsened functioning with olanzapine compared to placebo.

Conclusion: In this descriptive analysis of outpatients with Alzheimer's disease in usual care settings, some clinical symptoms improved with atypical antipsychotics. Antipsychotics may be more effective for particular symptoms, such as anger, aggression, and paranoid ideas. They do not appear to improve functioning, care needs, or quality of life.

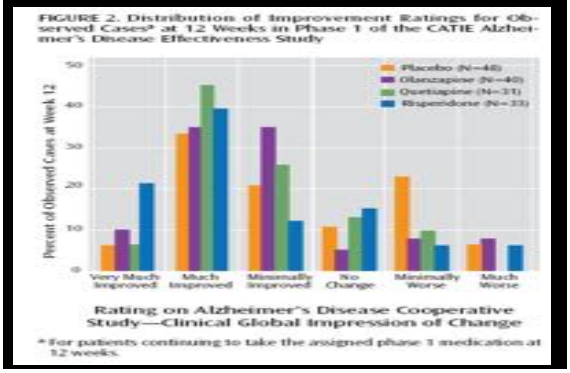
(Am J Psychiatry 2008; 165:844–854)

CATIE AD n=421, outpatients

FIGURE 1. Change in Clinical Symptoms for Observed Cases[a] in Phase 1 of the CATIE Alzheimer's Disease Effectiveness Study[b]



CATIE AD

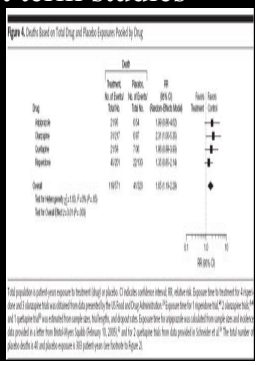


The problem…

- Data from 12-week RCTs have led to concerns about increased mortality in patients with Alzheimer's disease (AD) who are prescribed antipsychotics

Background: Short term studies

- Fifteen placebo controlled trials
  - (9 unpublished), generally 10 to 12 weeks, (aripiprazole [n=3], olanzapine [n=5], quetiapine [n=3], risperidone [n=5]).
- Pooled analysis
  - A total of 3353 patients were randomized to study drug and 1757 were randomized to placebo.
- Absolute risk difference
  - Death occurred more often among patients randomized to drugs (118 [**3.5%**] vs 40 [**2.3%**].
- JAMA. 2005



Health Canada / Santé Canada

Health Products and Food Branch
Direction générale des produits de santé et des aliments

- **Subject: INCREASED MORTALITY Associated with the Use of Atypical Antipsychotic Drugs in Elderly Patients with Dementia**
- *Dear Health Care Professional,*
  - *Health Canada is advising Canadians that treatment with atypical antipsychotic medication of behavioral disorders in elderly patients is associated with an increased risk for all-cause mortality.*
  - *Except for risperidone (RISPERDAL), these medications are not approved for use in elderly demented patients.*

The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial

Clive Ballard, Maria Luisa Hanney, Megan Theodoulou, Simon Douglas, Rupert McShane, Katja Kossakowski, Randeep Gill, Edmund Juszczak, Ly-Mee Yu, Robin Jacoby, for the DART-AD investigators

Summary

Background Data from 12-week placebo-controlled trials have led to mounting concerns about increased mortality in patients with Alzheimer's disease (AD) who are prescribed antipsychotics; however, there are no mortality data from long-term placebo-controlled trials. We aimed to assess whether continued treatment with antipsychotics in people with AD is associated with an increased risk of mortality.

Methods Between October, 2001, and December, 2004, patients with AD who resided in care facilities in the UK were enrolled into a randomised, placebo-controlled, parallel, two-group treatment discontinuation trial. Participants were randomly assigned to continue with their antipsychotic treatment (thioridazine, chlorpromazine, haloperidol, trifluoperazine, or risperidone) for 12 months or to switch their medication to an oral placebo. The primary outcome was mortality at 12 months. An additional follow-up telephone assessment was done to establish whether each participant was still alive 24 months after the enrolment of the last participant (range 24–54 months). Causes of death were obtained from death certificates. Analysis was by intention to treat (ITT) and modified intention to treat (mITT). This trial is registered with the Cochrane Central Registry of Controlled Trials/National Research Register, number ISRCTN33368770.

Findings 165 patients were randomised (83 to continue antipsychotic treatment and 82 to placebo), of whom 128 (78%) started treatment (64 continued with their treatment and 64 received placebo). There was a reduction in survival in the patients who continued to receive antipsychotics compared with those who received placebo. Cumulative probability of survival during the 12 months was 70% (95% CI 58–80%) in the continue treatment group versus 77% (64–85%) in the placebo group for the mITT population. Kaplan–Meier estimates of mortality for the whole study period showed a significantly increased risk of mortality for patients who were allocated to continue antipsychotic treatment compared with those allocated to placebo (mITT log rank p=0·03; ITT p=0·02). The hazard ratio for the mITT group was 0·58 (95% CI 0·35 to 0·95) and 0·58 (0·36 to 0·92) for the ITT population. The more pronounced differences between groups during periods of follow up longer than 12 months were evident at specific timepoints (24-month survival 46% vs 71%; 36-month survival 30% vs 59%).

Interpretation There is an increased long-term risk of mortality in patients with AD who are prescribed antipsychotic medication; these results further highlight the need to seek less harmful alternatives for the long-term treatment of neuropsychiatric symptoms in these patients.

Lancet Neurol 2009; 8: 151–57
Published Online January 9, 2009
DOI:10.1016/S1474-4422(08)70295-3

See Leading Edge page 125

Wolfson Centre for Age-Related Diseases, Wolfson Building, Guy's Campus, King's College London, London SE1 1UL, UK (C Ballard MD, K Kossakowski BSc, R Gill MRCPsych); Northgate Hospital, Morpeth, Northumberland, NE65 2RF, UK (M L Hanney PhD); Department of Psychiatry, University of Oxford, The Warneford Hospital, Oxford, UK (M Theodoulou MRCPsych, R Jacoby DM); Department of Psychiatry, Newcastle University, Newcastle upon Tyne, UK (S Douglas BSc); Oxfordshire and Buckinghamshire Mental Health NHS Trust and University of Oxford, Department of Psychiatry, Fellbrook Centre, Oxford, UK (R McShane MRCPsych); and Centre for Statistics in Medicine, University of Oxford, Oxford, UK (E Juszczak MSc, L-M Yu MSc)

Findings

- At 12 months
  - Cumulative probability of survival during the 12 months was **70%** (95% CI 58–80%) in the continue treatment group versus **77%** (64–85%) in the placebo group for the mITT population.
- After 12 months
  - Kaplan–Meier estimates of mortality for the whole study period showed a significantly increased risk of mortality for patients who were allocated to continue antipsychotic treatment compared with those allocated to placebo (mITT log rank p=0·03; ITT p=0·02).

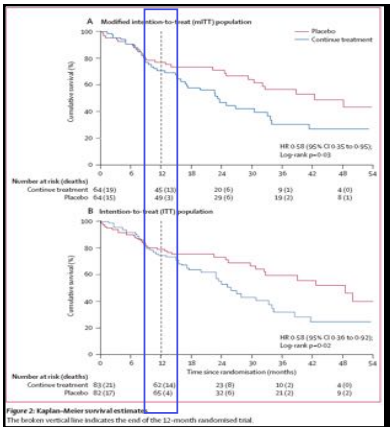


Figure 2: Kaplan–Meier survival estimates
The broken vertical line indicates the end of the 12-month randomised trial.

- Randomized Control Phase
  - 12 months
- Loss of control after.
  - Unclear details in both groups after aside from death by telephone interview and requests for death certificates

CCCDTD 2012

- Revised recommendation Risperidone, olanzapine and aripiprazole can be used for severe agitation, aggression and psychosis where there is risk of harm to the patient and/or others.
- The potential benefit of all antipsychotics must be weighed against the significant risks such as cerebrovascular adverse events and mortality. (Grade 2A)
  - *Previous recommendation Risperidone and olanzapine can be used for severe agitation, aggression and psychosis. The potential benefit of all antipsychotics must be weighed against the potential risks such as cerebrovascular adverse events and mortality.*

Herrmann et al. Alzheimer's Research & Therapy 2013, 5(Suppl 1):S5

CCCDTD 2012

- *Revised recommendation* There is insufficient evidence to recommend for or against the use of SSRIs or trazodone in the management of agitated patients. (Grade 2B)
  - *Previous recommendation There is insufficient evidence to recommend for or against the use of trazodone in the management of nonpsychotic, agitated patients.*

Herrmann et al. Alzheimer's Research & Therapy 2013, 5(Suppl 1):S5

BPSD: Antidepressants

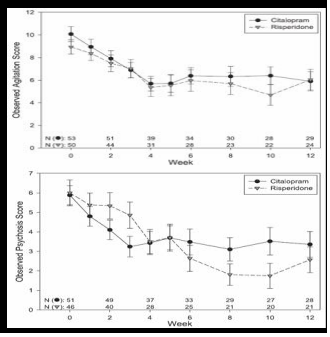
- Inconclusive evidence for Trazodone
- 2 RCTs showing similar efficacy of Risperidone to Citalopram and Escitalopram (not placebo controlled)
- 1 DBPRCT JAMA 2014

Double-Blind Comparison of Citalopram and Risperidone in BPSD
Pollock et al. AJGP 2007

TABLE 1. Baseline Participant Characteristics

Characteristic	Citalopram	Risperidone
N	53	50
Age (years)	82.0 (7.5)	81.5 (9.2)
Female, % (N)[a]	47.2 (25)	76.0 (38)
White, % (N)	81.1 (43)	82.0 (41)
Cumulative Illness Rating Scale-Geriatrics score	9.6 (3.0)	9.5 (4.5)
Mini Mental State Examination score	9.8 (8.5)	11.9 (8.4)
Median	7	11.5
Interquartile range	2-18	4.5-19.5
Severe Impairment Battery	63.9 (35.5)	71.4 (29.3)
Cornell Scale for Depression in Dementia	10.7 (11.8)	13.3 (16.2)
Delusions or hallucinations, % (N)	35.8 (19)	40.0 (20)
NBRS total score[b]	60.5 (16.8)	55.6 (15.6)
NBRS agitation score (items 8, 11, and 14)	10.1 (4.8)	8.9 (4.5)
NBRS psychosis score (items 16, 18, and 20)	5.9 (3.5)	6.0 (4.5)
NPI total score	40.8 (25.1)	34.4 (21.1)
UKU total score	13.7 (5.2)	12.1 (4.1)

Notes: Data are means (SD) unless noted.
[a]Significant difference between treatment groups: $\chi^2 = 9.00$, $df = 1$, $p = 0.003$.
[b]Significant difference between treatment groups: $t = 2.04$, $df = 94$, $p = 0.044$.

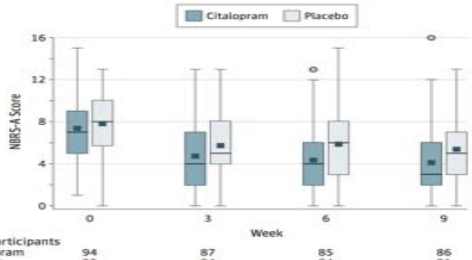


N=103, 12 week

Effect of Citalopram on Agitation in Alzheimer Disease
The CitAD Randomized Clinical Trial

n=186, 9 weeks, Placebo controlled flexible dose 10-30 mg

Figure 2. Neurobehavioral Rating Scale (NBRS)-Agitation Subscale



No. of participants				
Citalopram	94	87	85	86
Placebo	92	84	84	81

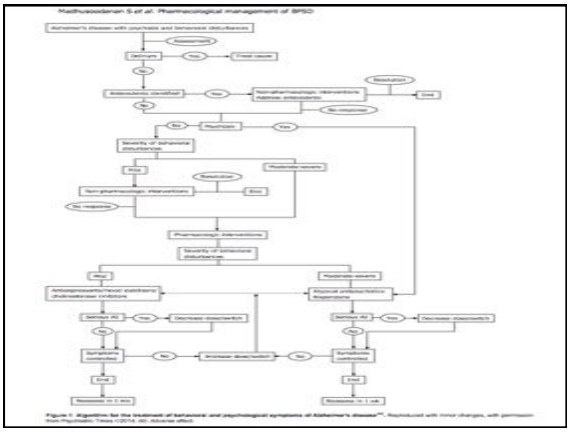
Higher NBRS scores indicate more severe symptoms. The horizontal bar inside the boxes indicates the median, the square in the boxes indicates the mean, and the lower and upper ends of the boxes are the first and third quartiles. The whiskers indicate values within 1.5 × the interquartile range from the upper or lower quartile (or the minimum and maximum if within 1.5 × the interquartile range of the quartiles) and data more extreme than the whiskers are plotted individually as outliers.

What about anticonvulsants [tegretol] and cognitive enhancers?

CCCDTD 2012

- New recommendation There is good evidence that valproate should not be used for agitation and aggression in AD. (Grade 1A)
- Revised recommendation There is insufficient evidence to recommend for or against the use of ChEIs and/or memantine for the treatment of neuropsychiatric symptoms as a primary indication. (Grade 2B)
  - Previous recommendation Patients who have mild to moderate AD and neuropsychiatric symptoms can be considered for a trial of a ChEI and/or memantine for these symptoms.

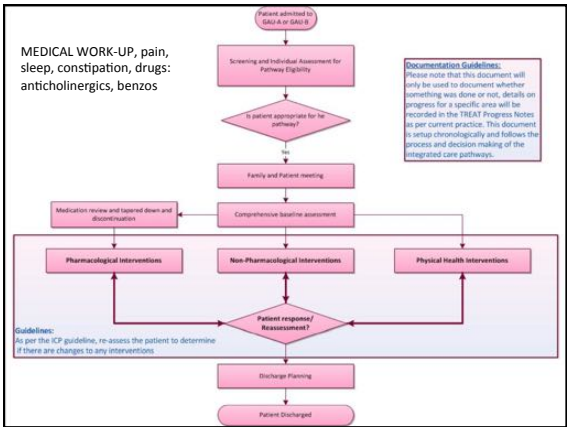
Herrmann et al. Alzheimer's Research & Therapy 2013, 5(Suppl 1):S5

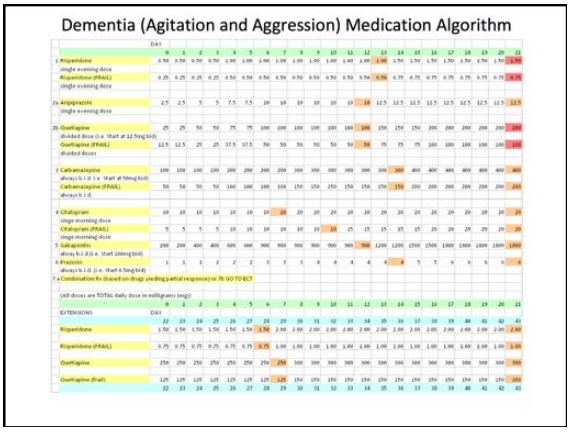


Agitation in Alzheimer's Dementia: An Integrated Pathway at CAMH

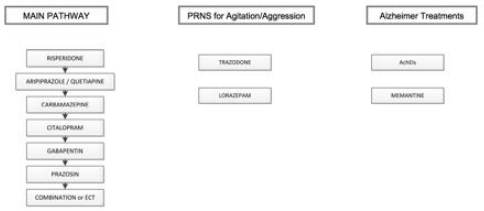
NBRHC Psychiatry CME rounds
February 25, 2014
Vincent Woo, MD, PhD, FRCPC
Head Inpatient Geriatrics and Dual Diagnosis
Geriatric Mental Health Services, CAMH

MEDICAL WORK-UP, pain, sleep, constipation, drugs: anticholinergics, benzos





Summary of Medications



One of the most common precipitants of delirium is medication. Numerous medications across many classes have been noted to precipitate delirium. The commonly used benzodiazepine lorazepam has been shown to independently increase delirium development in intensive care unit patients (Pandharipande et al. 2006; Figure 8–5).

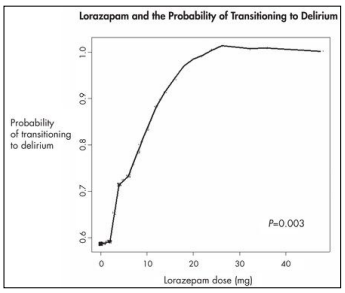


FIGURE 8–5. Lorazepam and the probability of transitioning to delirium.

Source. Reprinted from Pandharipande P, Shintani A, Peterson J, et al: "Lorazepam Is an Independent Risk Factor for Transitioning to Delirium in Intensive Care Unit Patients." *Anesthesiology* 104:21–26, 2006. Copyright 2006, Lippincott Williams & Wilkins. Used with permission.

Adverse Effects

- Antipsychotics
  - Cardiac (QTC and Torsades)
  - EPS (axial dystonia, tremor, gait instability, TD)
  - CVA
  - Sudden death
- SSRIs
  - Hyponatremia, balance, GI bleeds, cardiac (QTC)
- Mood Stabilizers
  - Hematologic, sedation, DDI
- AChEI
  - Activation, GI, Sleep, Cramps

What are some non-pharmacological approaches to BPSD?

NON-PHARMACOLOGICAL INTERVENTIONS

Allied Health Professional	NON-PHARMACOLOGICAL INTERVENTIONS IDENTIFIED INITIALLY AS MOST APPROPRIATE*			
Please check discipline:	Social Contact	Sensory Enhancement/ Relaxation	Purposeful Activity	Physical Activity
☐ Occupational Therapist ☐ Recreation Therapist ☐ Social Worker ☐ Primary Nurse Name: Sign: Date:	☐ Pet therapy ☐ One-to-one visit ☐ Other:_____	☐ Hand massage ☐ Individualized Music ☐ Individualized art ☐ Sensory modulation ☐ Other:_____	☐ Helping tasks / Volunteer role ☐ Inclusion in group programs of identified interest ☐ Access to outdoors ☐ Other:_____	☐ Exercise group ☐ Indoor/outdoor walks ☐ Individual exercise program ☐ Other:_____

*Physical health interventions and non-pharmacological interventions will be based on individual patient need, likes and dislikes.

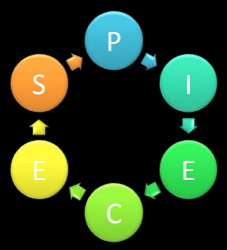
Goals of Care	Examples of psychological and social interventions
Reduce social isolation Stimulate the senses Promote relaxation Reduce agitation	• Talking and singing • Watching family videos • Pet therapy • Music • Sensory stimulation (e.g., Snoezelen room) • Aromatherapy • Bright light therapy • White noise • Massage and touch
Increase positive engagement with physical & social environment	• Recreational activities • Walking programs • Group exercise

Manage behaviours that may be disturbing, disruptive or potentially harmful

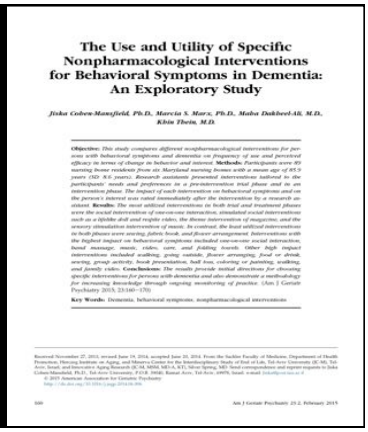
- The selection of specific behaviour therapy interventions should be based on analysis of the factors that are maintaining the behaviour (ABC Behavior Charting).
- Interventions may include reinforcing (rewarding) behaviours that are incompatible with problem behaviours and use of stimulus control (cueing) to encourage context-appropriate behaviours.
- Development and implementation of individualized behaviour therapy requires appropriate staff training and support (e.g., P.I.E.C.E.S.).

Approaches

- GPA
- "Stop and Go" care
- PIECES



Paper Discussion



The Use and Utility of Specific Nonpharmacological Interventions for Behavioral Symptoms in Dementia: An Exploratory Study

Jiska Cohen-Mansfield, Ph.D., Marcia S. Marx, Ph.D., Maha Dakheel-Ali, M.D., Khin Thein, M.D.

NPS Prospective Study

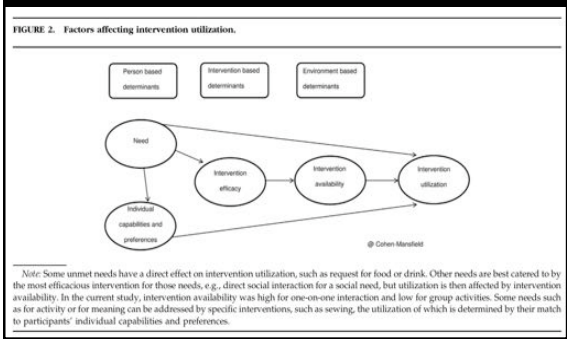


FIGURE 2. Factors affecting intervention utilization.

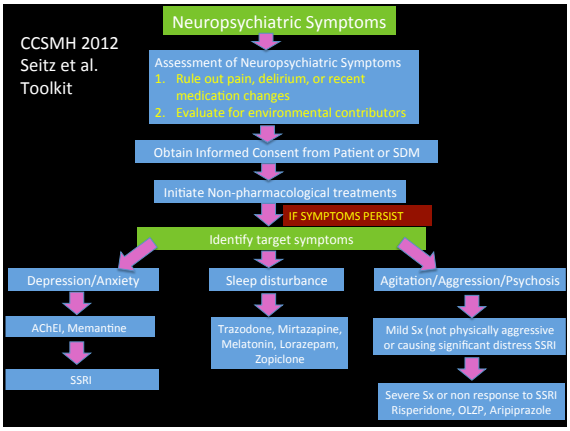
Note: Some unmet needs have a direct effect on intervention utilization, such as request for food or drink. Other needs are best catered to by the most efficacious intervention for those needs, e.g., direct social interaction for a social need, but utilization is then affected by intervention availability. In the current study, intervention availability was high for one-on-one interaction and low for group activities. Some needs such as for activity or for meaning can be addressed by specific interventions, such as sewing, the utilization of which is determined by their match to participants' individual capabilities and preferences.

Case 2

- An 78-year-old dentist. Developed seizures 3 years ago and Rx Epival. Followed by a Geriatric Medicine Service. Dx with Dementia, likely AD.
- Admitted to plastics for a large basal cell ca resection which was complicated by cellulitis. Became more confused. Increasingly combative. Hallucinating. Dx with DLB.
- Started on Neuroleptics/Trazodone.
- Put in a Broda continuously, striking out at staff injuring some of them. Largely either unconscious or agitated.

Case 3

- An 85-year-old woman with a gradual progression of memory problems. She has problems with her "nerves". She has been referred to your service with the request for admission.
- The main issues at the nursing home include:
  - *anxiety, crying, need for reassurance from staff repeatedly through the day, wandering at night, and hoarding of multiple items (paper, plastic cutlery, towels) in her room.*



Take home points

1. A comprehensive assessment is helpful in evaluating symptoms and defining treatment goals.
   - Scales can measure severity, frequency and timing of behaviour
2. BPSD is best managed by non-pharmacological means if possible.
   - Some behaviours are not amenable to medications
3. Severe BPSD may need both non-pharmacological and pharmacological means.
   - Pharmacological treatment needs to be appropriate and defined.
4. An individually tailored care plan works best that takes into account individual and environmental factors.