Depression in Dementia: Challenges in Diagnosis and Management

BrainXchange Webinar
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Disclosures

- Dr. Seitz
  - Advisory Board: Eli-Lilly (2013)
  - Research Grants: CIHR, Alzheimer's Association, SEAMO AFP Innovation Fund
- Dr. Kirkham has no conflicts of interest

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Objectives

- Understand the phenomenology and epidemiology of depression in dementia (DpD)
- Develop an approach to screening for and diagnosis of DpD
- Review the evidence for the treatment of DpD
- Discuss resources in Ontario for managing depressed older adults with dementia

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Depression in Dementia

- Among the non-cognitive symptoms of dementia
- Behavioral and Psychological Symptoms of Dementia (BPSD), neuropsychiatric symptoms (NPS), responsive behaviors

  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

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Depression in Dementia

- Depression is risk factor for development of Alzheimer's disease[1] and individuals with dementia are at higher risk for depression
  - Early-life depression→2x increased risk for late-life dementia[2]
  - Direction of causality?

1. Byers, Nature Rev Neurology, 2011
2. Enach, Curr Op in Psych, 2011

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Prevalence of Depressive Symptoms and Major Depression in Dementia

- Wide variation in estimates
- 20-30% of people with AD have depressive symptoms[1]
  - Vascular dementia and DLB 2 – 3X > Alzheimer's
- Few longitudinal studies on the course of DpD
  - Variable results

1. Enach, Curr Op in Psych, 2011

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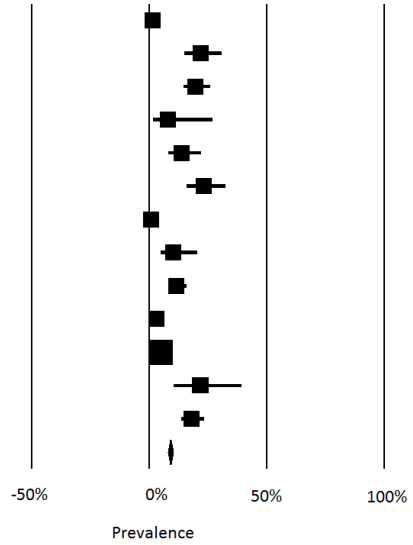
Prevalence of DpD

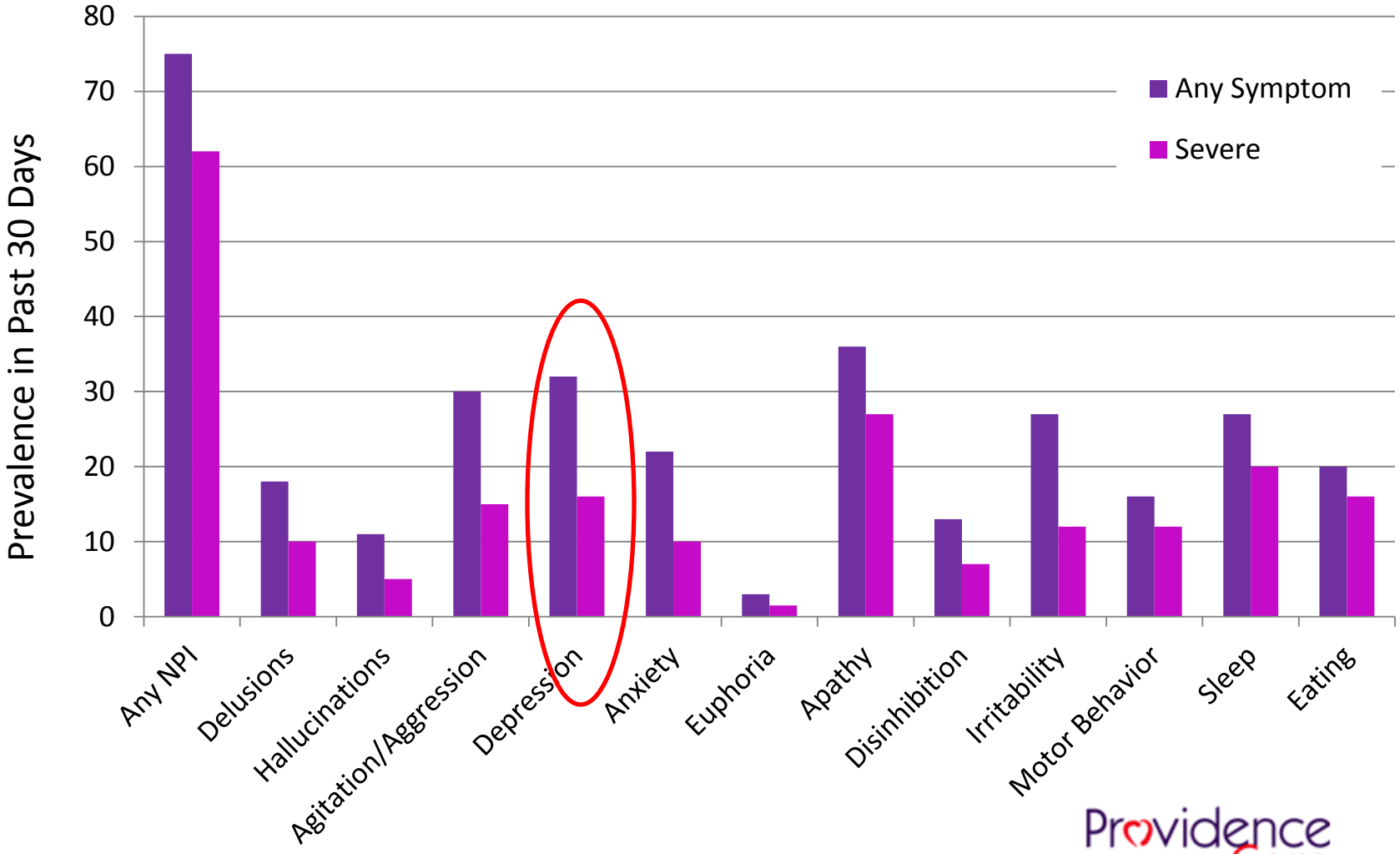
- Prevalence MDD in any dementia: 9.1% (8.2 to 10%)
- Alzheimer's disease: 5.1% (3.1% to 8.4%) vs. vascular dementia 15.5% (9.4% to 24.3%)

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Weiner, 1994	0.015	0.006	0.040	-8.285	0.000
Lyketsos, 1997	0.220	0.152	0.308	-5.471	0.000
Payne, 2002	0.199	0.149	0.260	-7.882	0.000
Ballard, 1996a	0.080	0.020	0.269	-3.313	0.001
Teng, 2008b	0.139	0.084	0.221	-6.344	0.000
Migliorelli, 1995	0.233	0.161	0.324	-5.112	0.000
Weiner, 2002a	0.009	0.003	0.028	-8.083	0.000
Reichman, 1995a	0.104	0.051	0.203	-5.379	0.000
Forsell, 1998	0.118	0.086	0.159	-11.356	0.000
Newman, 1999a	0.031	0.019	0.051	-13.099	0.000
Castilla-Puentes, 2010	0.051	0.044	0.059	-34.908	0.000
Rosen, 1991	0.219	0.108	0.393	-2.977	0.003
Zubenko, 2003	0.181	0.138	0.235	-9.059	0.000
Overall	0.091	0.082	0.100	-41.644	0.000



Asmer et al., CAGP, 2015

NPS in Alzheimer's Disease



Lyketsos, JAMA, 2002

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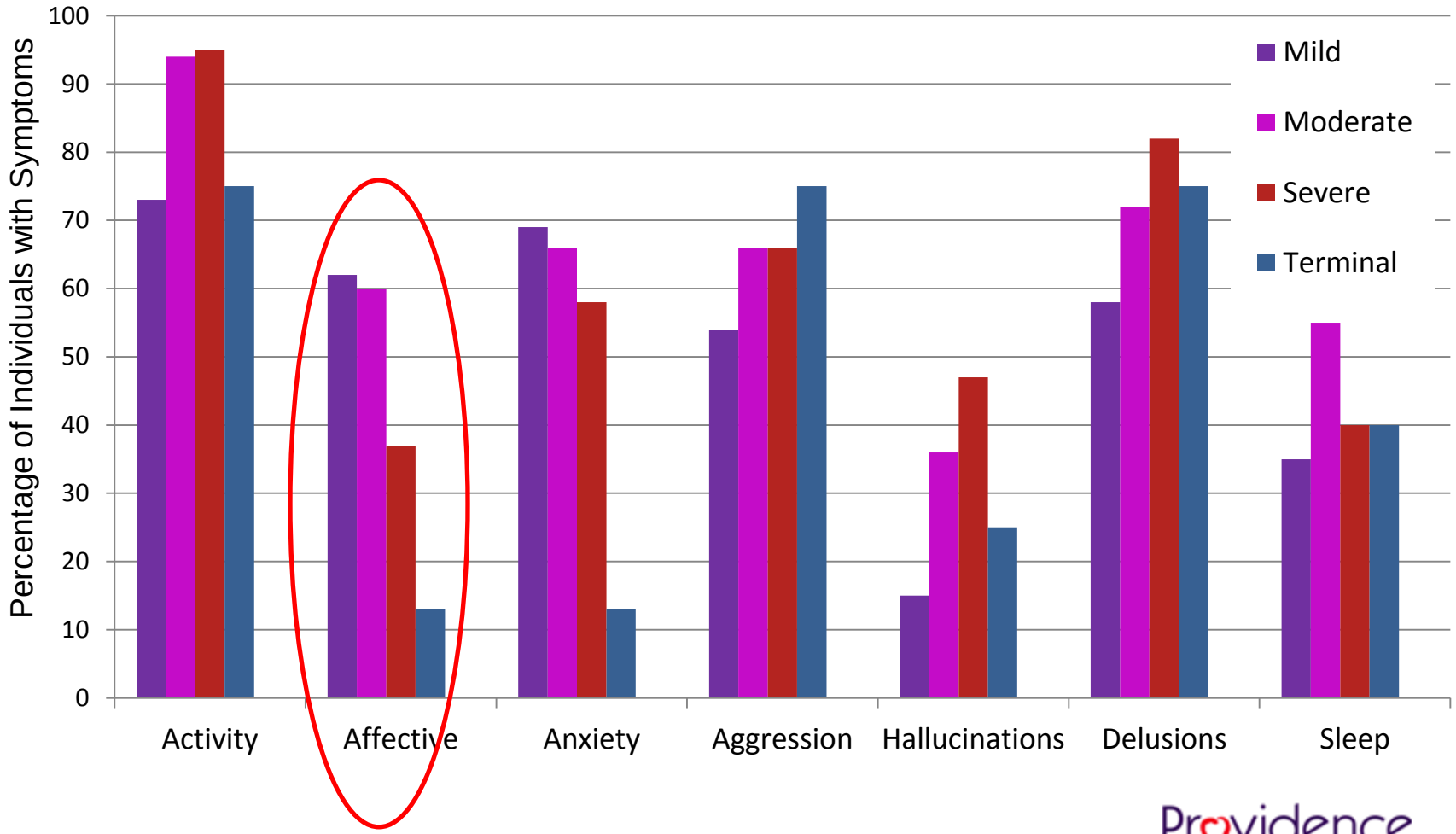
Associations with Stage of Illness



Chen, Am J Geriatr Psychiatry, 2000

Prevalence of NPS in Long-Term Care

- 60% of individuals LTC settings have dementia[1]
- Overall prevalence of NPS:
  - Median prevalence of any NPS: 78%
- Prevalence of NPS[2]:
  - Psychosis 15 – 30%
  - Depression: 30 – 50%
  - Physical agitation: 30%
  - Aggression: 10 – 20%

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

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Prevalence of NPS in LTC

BEHAVE – AD Items	Prevalence
Delusions	54%
Hallucinations	33%
Psychosis	60%
Aggression	77%
Activity Disturbance	53%
Diurnal Disturbance	47%
Affective Disturbance	60%
Anxiety	69%
Any BEHAVE-AD	92%

Brodaty, 2001; International Psychogeriatric Association BPSD Guide, 2011

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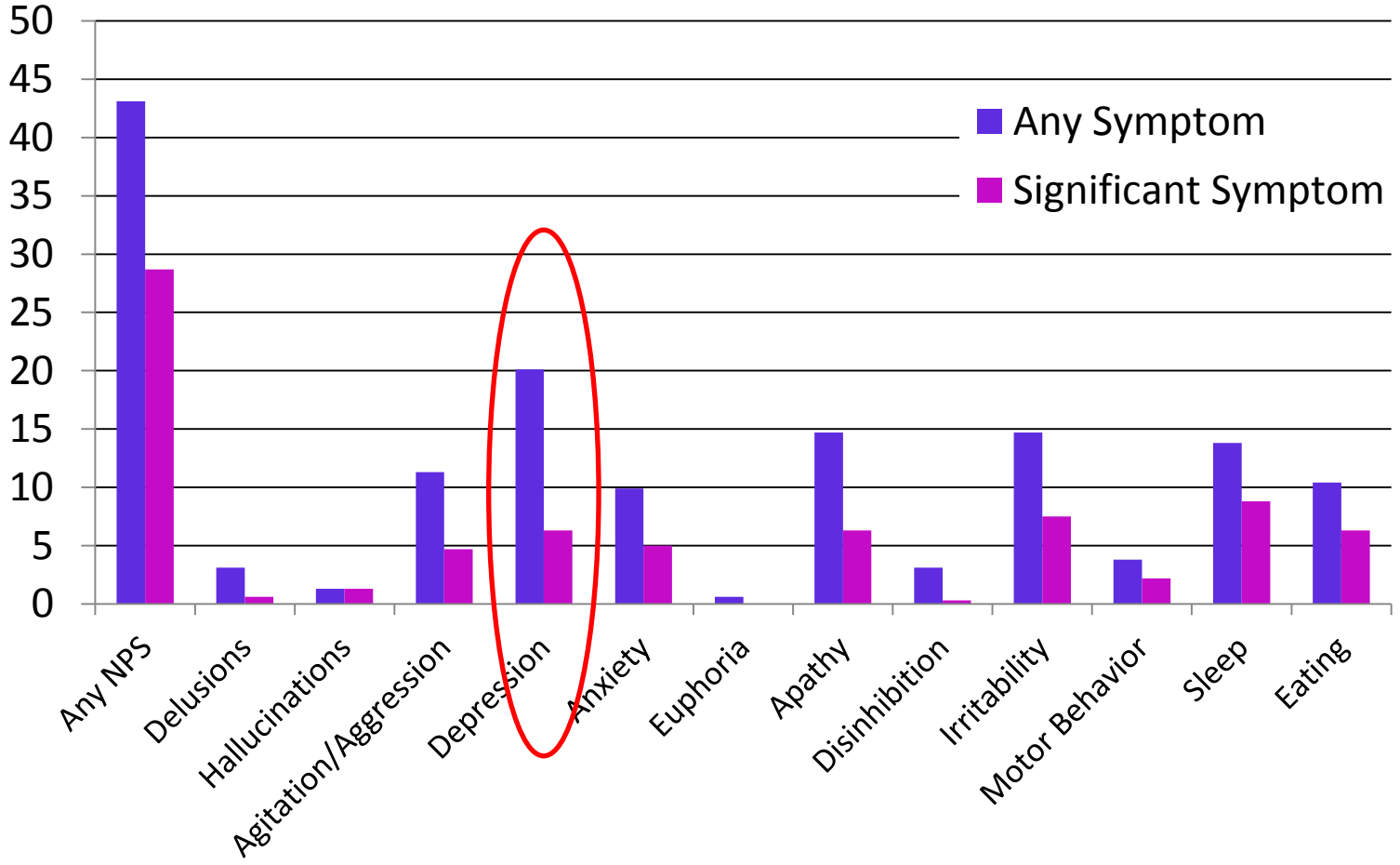
Prevalence of NPS in MCI



Lyketsos, JAMA, 2002

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NPS in MCI and AD Conversion

- Depression is predictor of conversion in MCI[1]
- Each symptom of anxiety in MCI increases risk of AD conversion by HR = 1.8[2]
  - Persistent worrying (HR = 5.3), decision making (HR = 5.6)
  - MCI Conversion over 3 years:
    - No anxiety: 40.9%
    - Anxiety: 83.3%
- MCI with apathy associated with 6.9X increased risk of conversion[3]

1. Gabryelewicz, Int J Geriatr Psychiatry, 2007
2. Palmer, Neurology, 2007
3. Palmer, J Alz Dis, 2010

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Persistence of NPS

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

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

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Management

- Assessment
- Nonpharmacological
- Pharmacological

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Challenges: Diagnosis of DpD

- Depression screening instruments not well validated in dementia
  - Deficits in awareness, communication skills may influence questionnaires and symptom reporting[1]
- Overlap between symptoms of depression and symptoms of dementia
  - Apathy, decreased interest, fatigue
- Older adults report fewer affective symptoms[2]
  - "Depression without sadness"

1. Enach, Curr Op in Psych, 2011
2. Hochang, Biol Psychiary, 2003

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Diagnosing Depression in Dementia

- Similar to diagnosing depression in individuals without dementia
- Two week period of **three or more symptoms** of (one of first two required):
  - **Depressed mood**
  - **Decreased positive affect or pleasure in response to social contacts and usual activities**
  - Disruption of sleep
  - Disruption of appetite
  - Psychomotor changes
  - Irritability
  - Fatigue or loss of energy
  - Feelings of worthlessness, hopelessness, or excessive guilt
  - Recurrent thoughts of death, suicidal ideation or plan
- Criteria also met for dementia of the Alzheimer Type
- Symptoms cause distress and not caused by other conditions or substances

Teng, Am J Geriatr Psychiatry, 2008

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Measuring Depression in Dementia

- Cornell Scale for Depression in Dementia
- Based on informant interview *and* patient observation over the preceding week
- Items scored from 0=absent, 1=mild, 2=severe
- 19 items
- Items include mood-related items, behavioral changes, physical changes, activity cycle, and negative ideation

Alexopolous, Biol Psychiatry, 1988

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Cornell Scale for Depression in Dementia

Name_____ Age _____ Sex _____ Date _____

Inpatient Nursing Home Resident Outpatient

Scoring System

A = unable to evaluate 0 = absent 1 = mild or intermittent 2 = severe

Ratings should be based on symptoms and signs occurring during the week prior to interview. No score should be given in symptoms result from physical disability or illness.

A. Mood-Related Signs				
1. Anxiety: anxious expression, ruminations, worrying	a	0	1	2
2. Sadness: sad expression, sad voice, tearfulness	a	0	1	2
3. Lack of reactivity to pleasant events	a	0	1	2
4. Irritability: easily annoyed, short-tempered	a	0	1	2
B. Behavioral Disturbance				
5. Agitation: restlessness, handwringing, hairpulling	a	0	1	2
6. Retardation: slow movement, slow speech, slow reactions	a	0	1	2
7. Multiple physical complaints (score 0 if GI symptoms only)	a	0	1	2
8. Loss of interest: less involved in usual activities (score only if change occurred acutely, i.e. in less than 1 month)	a	0	1	2
C. Physical Signs				
9. Appetite loss: eating less than usual	a	0	1	2
10. Weight loss (score 2 if greater than 5 lb. in 1 month)	a	0	1	2
11. Lack of energy: fatigues easily, unable to sustain activities (score only if change occurred acutely, i.e., in less than 1 month)	a	0	1	2
D. Cyclic Functions				
12. Diurnal variation of mood: symptoms worse in the morning	a	0	1	2
13. Difficulty falling asleep: later than usual for this individual	a	0	1	2
14. Multiple awakenings during sleep	a	0	1	2
15. Early morning awakening: earlier than usual for this individual	a	0	1	2
E. Ideational Disturbance				
16. Suicide: feels life is not worth living, has suicidal wishes, or makes suicide attempt	a	0	1	2
17. Poor self esteem: self-blame, self-depreciation, feelings of failure	a	0	1	2
18. Pessimism: anticipation of the worst	a	0	1	2
19. Mood congruent delusions: delusions of poverty, illness, or loss	a	0	1	2

CSDD Scores:

≥ 9 MDD

≥ 13 severe depression

Sensitivity: 80 – 90%

Specificity: 70 – 80%

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Measuring Depression in Dementia

- Other scales:
  - Geriatric Depression Scale
  - Hamilton Rating Scale for Depression
  - Montgomery-Asberg Depression Rating Scale

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Assessment

History

- Past psychiatric history
  - Depression, bipolar disorder, anxiety
  - Prior treatments
- Past Medical History:
  - Conditions that may be affected by treatments
  - Diseases that may increase risk of depression (e.g. Parkinson's disease, stroke)

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Management of DpD

- Differential Diagnosis:
  - Delirium (especially hypoactive)
  - Pain or discomfort
  - Other medical causes
  - Environment causes

1. Sink, JAMA, 2005

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Assessment

Medication use potentially related to depression:

- Methyldopa
- Benzodiazepines
- Propranolol
- Reserpine
- Steroids
- Anti-Parkinsonian drugs
- β blockers
- Cimetidine
- Clonidine
- Hydralazine
- Oestrogens
- Progesterone
- Tamoxifen
- Vinblastine
- Vincristine
- Dextropropoxyphene

Medical conditions potentially related to depression:

- Endocrinopathy—hypothyroidism, hyperthyroidism, hypoparathyroidism, hyperparathyroidism, hypoadrenocorticism, hyperadrenocorticism, Cushing's disease
- Malignant disease—leukaemia, lymphoma, pancreatic cancer
- Cerebrovascular disease—lacunar infarcts, stroke, vascular dementia
- Myocardial infarction
- Metabolic disorder—B12 deficiency, malnutrition

Alexopoulos, Lancet, 2005

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Nonpharmacological Interventions for NPS

- Training caregivers or staff in behavioral management strategies and communication
- Mental health consultations
- Participation in pleasant events
- Exercise
- Music
- Sensory stimulation

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

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General Interventions for Depressive Symptoms

- Staff training approaches to improve engagement in pleasant activities
- Small RCTs of reminiscence therapy[1], validation therapy for LTC residents
- AD-Venture, wheelchair bicycling for LTC residents with dementia and depression[2]
- “Simple Pleasures” interventions improved affect and engagement in dementia[3]

1. Goldwasser, Int J Aging Hum Dev, 1987
2. Buettner L, Am J Alz Dis Other Dement, 2002
3. Buettner L, Am J Alz Dis, 1999

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Interventions for Depression

- Training family caregivers in behavioral therapy in either pleasant event scheduling or problem-solving approaches reduces depression in both patients and caregivers[1]
- Caregiver training in behavioral management and regular exercise (Reducing Disability in Alzheimer Disease) reduces depression and improves function

1. Teri, J Gerontol B Psycholog Sci Soc Sci, 1997
2. Teri, JAMA, 2003

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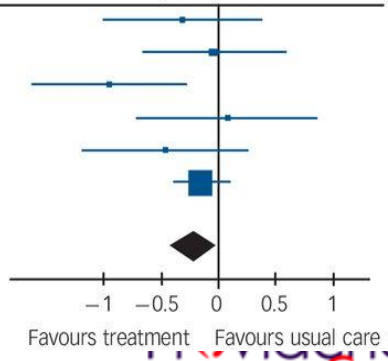
Psychotherapy Treatments for DpD

- 6 randomized controlled trials[1]
  - Based on various models (CBT, IPT, counselling)
- Overall, psychotherapy more effective than control conditions (d=0.22, 0.03 to 0.41, P=0.02)
- No effect on secondary outcomes, such as ADLs, quality of life, cognition, or caregiver depression

	Experimental			Control				Standardised mean difference	Standardised mean difference
Study or subgroup	Mean	s.d.	Total	Mean	s.d.	Total	Weight	IV, fixed, 95% CI	IV, fixed, 95% CI
Burgener *et al*[33]	3.3	2.9	19	4.3	3.4	14	7.4%	−0.31 (−1.01, 0.38)	
Burns *et al*[34]	5.4	2.6	20	5.5	3.1	20	9.3%	−0.03 (−0.65, 0.59)	
Spector *et al*[35]	10.38	5.835	21	16.72	7.283	18	8.0%	−0.95 (−1.62, −0.28)	
Stanley *et al*[36]	8.2	2.86	11	7.8	5.95	15	5.9%	0.08 (−0.70, 0.86)	
Tappen & Williams[37]	15.13	9.54	15	19.13	7.37	15	6.8%	−0.46 (−1.18, 0.27)	
Waldorff *et al*[38]	5.05	4.61	130	5.77	5.07	141	62.7%	−0.15 (−0.39, 0.09)	
Total (95% CI)			216			223	100.0%	−0.22 (−0.41, −0.03)	

Heterogeneity: $\chi^2 = 6.33$, d.f. = 5 ($P = 0.28$); $I^2 = 21\%$

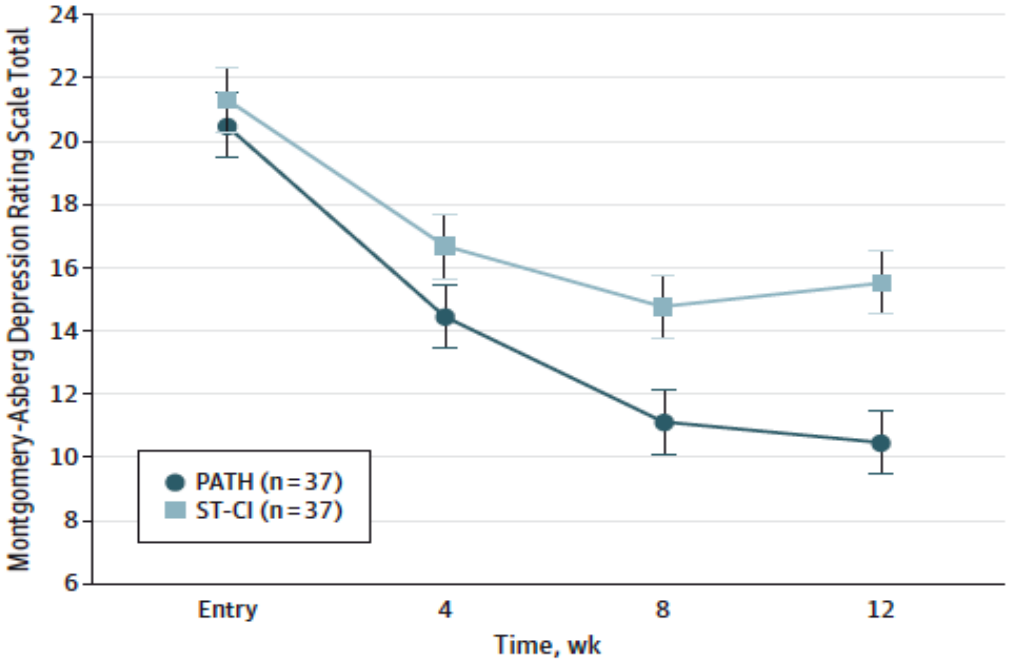
Test for overall effect: $Z = 2.30$ ($P = 0.02$)



1. Ortega, B J Psych, 2015

Problem Solving Therapy

- PATH=problem-solving therapy approach
  - compensatory strategies, environmental adaptations, and caregiver participation
- Participants with at least mild cognitive impairment, MMSE >17
- Remission rate = 38% vs 14% vs. supportive therapy



Kiosses, JAMA Psychiatry, 2015.

Antidepressants for DpD

- 11 randomized controlled trials[1]
- 5 positive, 6 negative studies
  - SSRIs: sertraline, citalopram, fluoxetine
  - SNRIs: venlafaxine
  - Other: mirtazapine, moclobemide, maprotiline, imipramine, clomipramine

1. Enach, Curr Op in Psych, 2011

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Antidepressants for DpD

- 2 meta-analyses of antidepressants for depression in dementia failed to find statistically significant benefits over placebo:
  - Nelson et al[1] (N=7 studies):
    - Response OR: 2.12 (0.95 – 4.70)
    - Remission OR: 1.97 (0.85 – 4.55)
    - Adverse event rates relatively low: 9% vs. 6% with placebo
  - Bains et al[2] (N=4 studies)
    - Weak support for efficacy of antidepressants

1. Nelson, J Am Geriatr Soc, 2011
2. Bains et al., Cochrane Syst Rev, 2002

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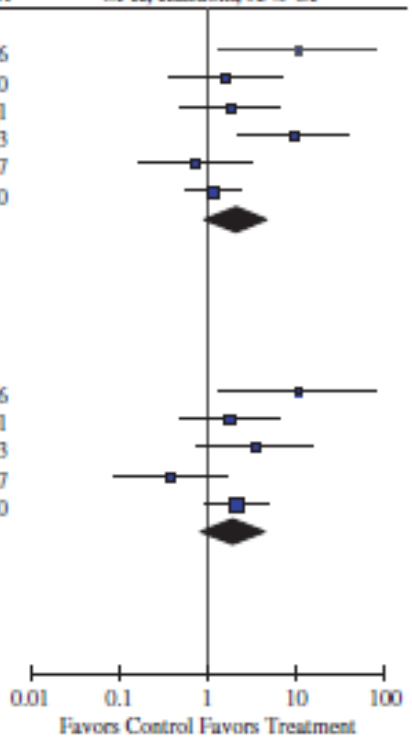
Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
A. Response Rates							
Petracca 1996[a,c]	9	11	3	10	10.3%	10.50 [1.36, 81.05]	1996
Magai 2000[b,d]	8	17	5	14	15.5%	1.60 [0.38, 6.82]	2000
Petracca 2001[b,d]	8	17	8	24	17.5%	1.78 [0.50, 6.37]	2001
Lyketsos 2003[a,d]	20	24	7	20	15.9%	9.29 [2.26, 38.15]	2003
de Vasconcelos Cunha 2007[b,d]	8	14	11	17	15.4%	0.73 [0.17, 3.11]	2007
Rosenberg 2010[a,c]	27	67	24	64	25.4%	1.13 [0.56, 2.27]	2010
Subtotal (95% CI)		**150**		**149**	**100.0%**	**2.12 [0.95, 4.70]**	
Total events	80		58				
Heterogeneity: $Tau^2 = 0.52$; $Chi^2 = 11.26$, df = 5 (P = 0.05); $I^2 = 56\%$							
Test for overall effect: Z = 1.84 (P = 0.07)							
B. Remission Rates							
Petracca 1996[b,c]	9	11	3	10	12.0%	10.50 [1.36, 81.05]	1996
Petracca 2001[b,d]	8	17	8	24	21.3%	1.78 [0.50, 6.37]	2001
Lyketsos 2003[a,d]	9	24	3	20	18.2%	3.40 [0.77, 14.93]	2003
de Vasconcelos Cunha 2007[b,d]	5	14	10	17	18.4%	0.39 [0.09, 1.67]	2007
Rosenberg 2010[b,d]	22	67	12	64	30.2%	2.12 [0.94, 4.76]	2010
Subtotal (95% CI)		**133**		**135**	**100.0%**	**1.97 [0.85, 4.55]**	
Total events	53		36				
Heterogeneity: $Tau^2 = 0.43$; $Chi^2 = 7.90$, df = 4 (P = 0.10); $I^2 = 49\%$							
Test for overall effect: Z = 1.59 (P = 0.11)							



1. Nelson, J Am Geriatr Soc, 2011

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HTA-SADD Study

- RCT of sertraline, mirtazapine and placebo in mild to moderate dementia (N=326)[1]
- No benefit for either drug over placebo on depression outcomes, all groups improved
- Some early benefit for mirtazapine over sertraline on behavioral symptoms and caregiver quality of life
- Higher adverse event rates for sertraline (GI) and mirtazapine (drowsiness) compared to placebo

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1. Banerjee, Lancet, 2011

Discontinuing Antidepressants

- RCT of antidepressant discontinuation in LTC residents without major depression in Norway (N=128)
- Increase in depressive symptoms at week 25
  - 2 point difference on CSDD (6 vs 4, p =0.04)
  - > 30% deterioration in CSDD: 54% discontinuation vs. 29% continued, *P*=0.006
  - Less severe baseline depressive symptoms associated with greatest deterioration

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1. Bergh, BMJ, 2012

Antidepressants for Other NPS

- 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

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Selective Serotonin Reuptake Inhibitors

- No significant difference noted between SSRIs and typical antipsychotics[1] or citalopram compared to risperidone[2] on NPS
- Similar results found for escitalopram (10 mg daily) compared to risperidone[3]

1. Seitz, Cochrane Database Syst Rev, 2011
2. Pollock, Am J Geriatr Psychiatry, 2007
3. Barak, Int Psychogeriatric, 2011

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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

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Future Directions

- Additional studies of psychotherapy and non-pharmacological treatments for DpD
- Further evaluation of pharmacological treatments for DpD
- ***Optimizing detection of DpD in routine clinical practice using depression rating scales***

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Depression rating scales for diagnosis of depression in older adults with Alzheimer's disease or related dementia (Protocol)

Seitz DP, Quinn TJ, Takwoingi Y, Gill SS, Lanctôt KL, Herrmann N, Rochon P, Kirkham JG, Rapoport M, Maxwell CJ

THE COCHRANE COLLABORATION®

Diagnostic Test Accuracy of Depression Screening Tools for Diagnosing DpD

- Canadian Institutes of Health Research Knowledge Synthesis Grant (2015 – 2016)
- Objectives:
  - 1.) Complete a systematic review and meta-analysis of the accuracy of depression ratings scales for the diagnosis of depression in dementia (DpD);
  - 2.) Examine factors that may impact on the accuracy of depression rating scales that are used to diagnose depression; and,
  - 3.) Create knowledge tools to assist clinicians with diagnosing DpD in routine clinical settings.

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DpD DTA Review Methods

- Cochrane Review supported through Cochrane Dementia and Cognitive Improvement Group Electronic database search for relevant articles through Cochrane
- Inclusion Criteria:
  - Validated criteria for dementia (e.g. DSM-IV, NINDS-ADRDA)
  - Validated reference standard for MDD (e.g. DSM, DpD criteria)
  - Index test including standard depression rating scales (e.g. HRSD) or scales specific for DpD

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DpD DTA Review Methods

- QUADAS-2 assessment for quality of included studies
- Data Extraction:
  - Age, gender, severity of cognitive impairment, type of dementia, residence of participants, criteria and type of dementia, reference standard and index test for DpD
  - TP, TN, FP, FN recorded in 2 X 2 tables for each tool at reported cut-points
- Meta-analysis:
  - Pooled sensitivity and specificity
  - Hierarchical summary ROC for multiple cut-points
  - Assess relative accuracy of scales using regression

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Knowledge Translation

- Cochrane Systematic Review
  - Protocol under review, complete review anticipated March 2016
- Creation of DpD online probability calculator

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Guidelines

Alexopolous**,** *Postgrad Med,* 2005	Herrmann, *CMAJ,* 2008
AAGP, *Am J Geriatr Psychiatry,* 2006	NICE-SICE, *Dementia Guideline,* 2007
APA, 2007 (online)	Royal Australian and New Zealand College of General Practitioners, 2006
Mulsant et al, J Nutr Health Aging, 2006	Royal Australian and New Zealand College of Psychiatrists, 2009
British Columbia Medical Association, 2008	Royal College of Psychiatrists, 2005
CCSMH, Assessment and Treatment of Mental Health Issues in LTC, 2006	Salzman et al., *J Clin Psychiatry*, 2008
Dettmore, *Geriatric Nursing*, 2009	Scottish Intercollegiate Guidelines Network, 2006
Fletcher, Evidence-Based Geriatric Nursing, 2008	

Vickland, Int Psychogeriatr, 2012

Resources

- Canadian Coalition for Seniors' Mental Health
  - www.ccsmh.ca
- International Psychogeriatrics Association BPSD Guides
  - http://www.ipa-online.net/ipaonlinev4/main/programs/task/task_BPSD.html

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Local Resources

- Alzheimer Society
- Geriatric Psychiatry Programs
  - Providence Care
- Geriatric Medicine Programs
  - Providence Care

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  - CAGP (Mark Rapoport)
  - Dr. Ken Le Clair and Jillian Dahm-McConnell (brainXchange)

- Cochrane Collaboration
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  - Sue Marcus (CDCIG)

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Conclusions

- Depressive symptoms and MDD are common among older adults with dementia
- Nonpharmacological interventions should be considered first-line treatments for DpD
- Evidence for antidepressants is still developing
- Several screening tools may be helpful for identifying DpD but further information required to optimize in routine practice

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Thank You

Dr. Dallas Seitz

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Dr. Julia Kirkham

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Survey

- Please take a few minutes to complete a short survey to help us better understand what tools would be helpful in identifying DpD:

- https://www.surveymonkey.com/r/3QZ8WK7

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