

Clinical aspects of depression and cognitive impairment

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Typical presentations

- 78 year old woman with Alzheimer's disease who is paranoid that others are stealing from her.
- 69 year old man with Lewy Body dementia who is agitated and physically aggressive when his wife tries to assist him with dressing and bathing.
- 72 year old woman with vascular dementia and history of a recent stroke who is withdrawn and refusing to participate in physical rehabilitation

Upshot: The many faces of depression

- Agitation and aggression
- Irritability
- Somatic symptoms
- Paranoia and psychosis
- Delayed rehabilitation
- Conflicts with caregiver
- Refusal to eat

Depression in dementia risk factors

- Family history of mood disorder
- History of mood disorder
- Female gender
- Earlier dementia stage
- Insight
- Younger age of onset
- Chronic pain

Depression and dementia

- Dementia as pseudodementia
 - Cognitive impairment common in depression
- Depression as prodrome
 - Higher dementia risk in depression with reversible cognitive dysfunction
- Depression as risk factor for dementia
 - Community studies show evidence
- Depression as psychological response
 - More depression in milder dementia

Why intervene?

- Increased cognitive impairment
- Excess disability
- Higher physical aggression
- Increased risk of institutionalization
- Elevated caregiver depression and burden
- Lower quality of life

Diagnosis of Depression

Depression in dementia: barriers to diagnosis

- Natural history poorly defined
- No “gold standard” or diagnostic criteria
- Dementia symptoms overlap with depression
- Phenomenology of depression in dementia differs from DSM-IV MDD

NIHM Provisional Criteria

(3 symptoms during a 2 week period)

- Significantly depressed mood: sad, hopeless, discouraged, tearful
- Decreased positive affect or reduced pleasure in response to social contacts and usual activities
- Social isolation or withdrawal
- Disruption in appetite not due to medical

NIMH Provisional Criteria (cont'd)

- Disruption in sleep
- Agitation or slowed behavior
- Irritability
- Fatigue or loss of energy
- Feelings of worthlessness or hopelessness, or inappropriate or excessive guilt
- Recurrent thoughts of death, or suicidal thoughts, or suicide plan/attempt

Tools for depression assessment

- Self administered:
 - CES-D,
 - Geriatric Depression Scale (GDS),
 - Neuropsychiatric Inventory Short Form
- Clinician administered
 - Cornell Depression Scale
 - Neuropsychiatric Inventory
 - Hamilton depression scale Self

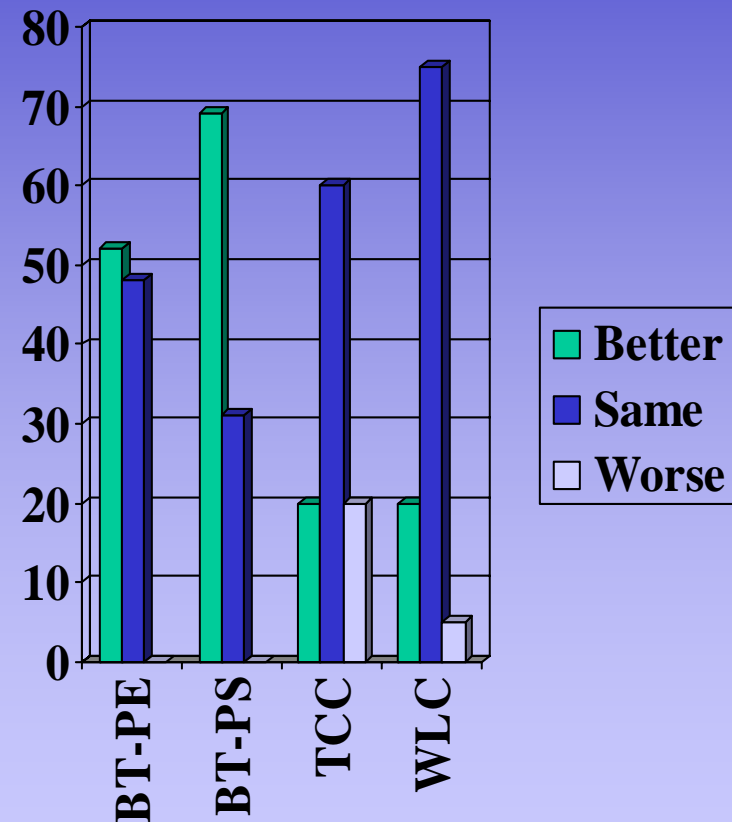
Key principles in depression diagnosis

- Know that depression can underpin wide range of behavioral disturbance
- Depression diagnosis in person with dementia is different
- Evaluate depression on spectrum of severity
- Incorporate multiple sources of information
- Consider standard rating scales

Treatment of depression

Nonpharmacological Intervention

- RCT
 - Pleasant events PE (n=23)
 - Problem solving PS (n=19)
 - Typical care TCC (n=10)
 - Wait list control WLC (n=20)
- 72 patients AD + mild to moderate depression
- 16 weeks
- Teri et al, 1997
- BT: caregiver and patient depression improved



Nonpharmacological: Reducing caregiver distress

- Does reducing caregiver distress lessen severity of depression and other behavioral symptoms?
- Several studies suggest an impact of caregiver interventions or distress on care recipient mood and behavior.
- Reducing caregiver distress may improve patient depression.
- Caregiver -- care recipient dyad is dynamic.

Antidepressant studies: Summary

- 12 double-blind drug trials (1989-2003)
- Antidepressants include TCAs and SSRI
- Duration 4-12 weeks
- Depressive symptoms or MDD
- In 10 double-blind placebo controlled, 6 favored active drug and none PBO
- High placebo response

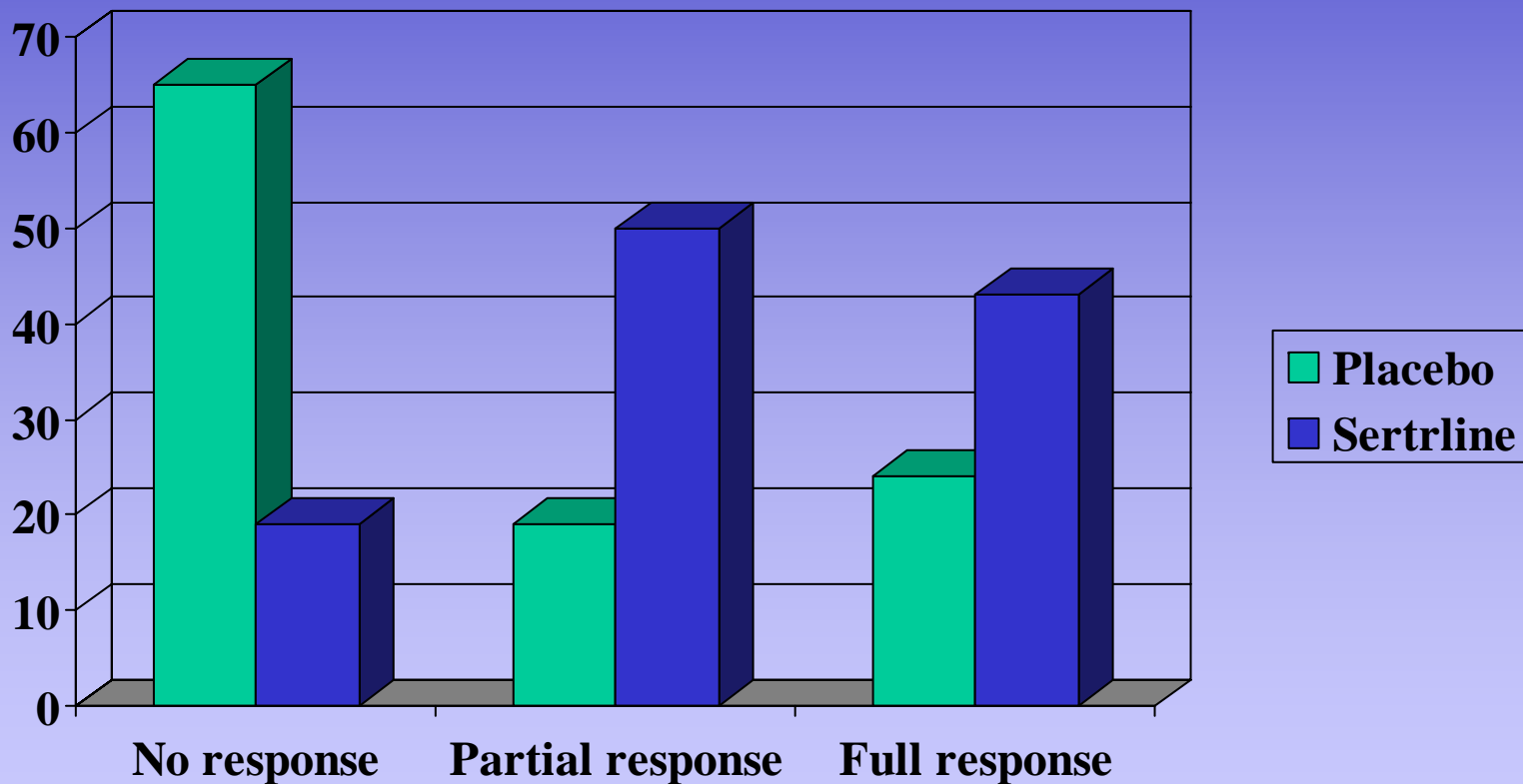
Placebo controlled trials

Study (n)	Indication	Drug	Duration	Outcome
Reifler 1989 (n=28)	MDD or dysthymia	Imipramine	8 weeks	Drug = PBO
Nyeth 1990 (n=98)	Depressive symptoms	Citalopram	4 weeks	Drug > PBO
Olafsson 1992 (n=46)	Depressive symptoms	Fluvoxamine	6 weeks	Drug = PBO
Nyeth 1992 (n=29)	Depressive	Citalopram	6 weeks	Drug > PBO
Petracca 1996 (n=21)	Depressive symptoms	Clomipramine	6 weeks	Drug > PBO

Placebo controlled trials

Study (n)	Indication	Drug	Duration	Outcome
Roth 1996 (n=28)	Depressive symptoms (HAM-D)	Moclobemide	8 weeks	Drug > PBO
Lyketsos 2003 (n=44)	MDD	Sertraline	12 weeks	Drug > PBO
Finkel 2004 (n=144)	Depressive symptoms	Sertraline	12 weeks	Drug > PBO
Petracca 2001 (n=41)	MDD or minor depression	Fluoxetine	6 weeks	Drug = PBO

Dementia in Alzheimer's Disease Study (Lyketsos et al, 2003)



Antidepressant treatment algorithm

- Initiate SSRI and titrate to target dose
- 4-6 weeks
 - If some improvement, increase
 - If no improvement, switch class (e.g. bupropion, mirtazapine)
- 10-12 weeks
 - If remission, continue
 - If some improvement, augment
- Treatment resistant: venlafaxine, remeron, wellbutrin, nortriptyline, MAOI, stimulants, ECT

Mulsant et al, Int J Ger Psychiatry 2001

Caveats on use of antidepressants

- SSRI
 - SIADH, withdrawal (paroxetine), serotonin syndrome
 - drug interactions (paroxetine, fluoxetine)
 - long half-life: fluoxetine
- Mirtazapine
 - sedation and increased appetite
- Venlafaxine and bupropion
 - increased BP, more activating
 - bupropion: lowers seizure threshold
- TCA
 - avoid tertiary amines
 - EKGs

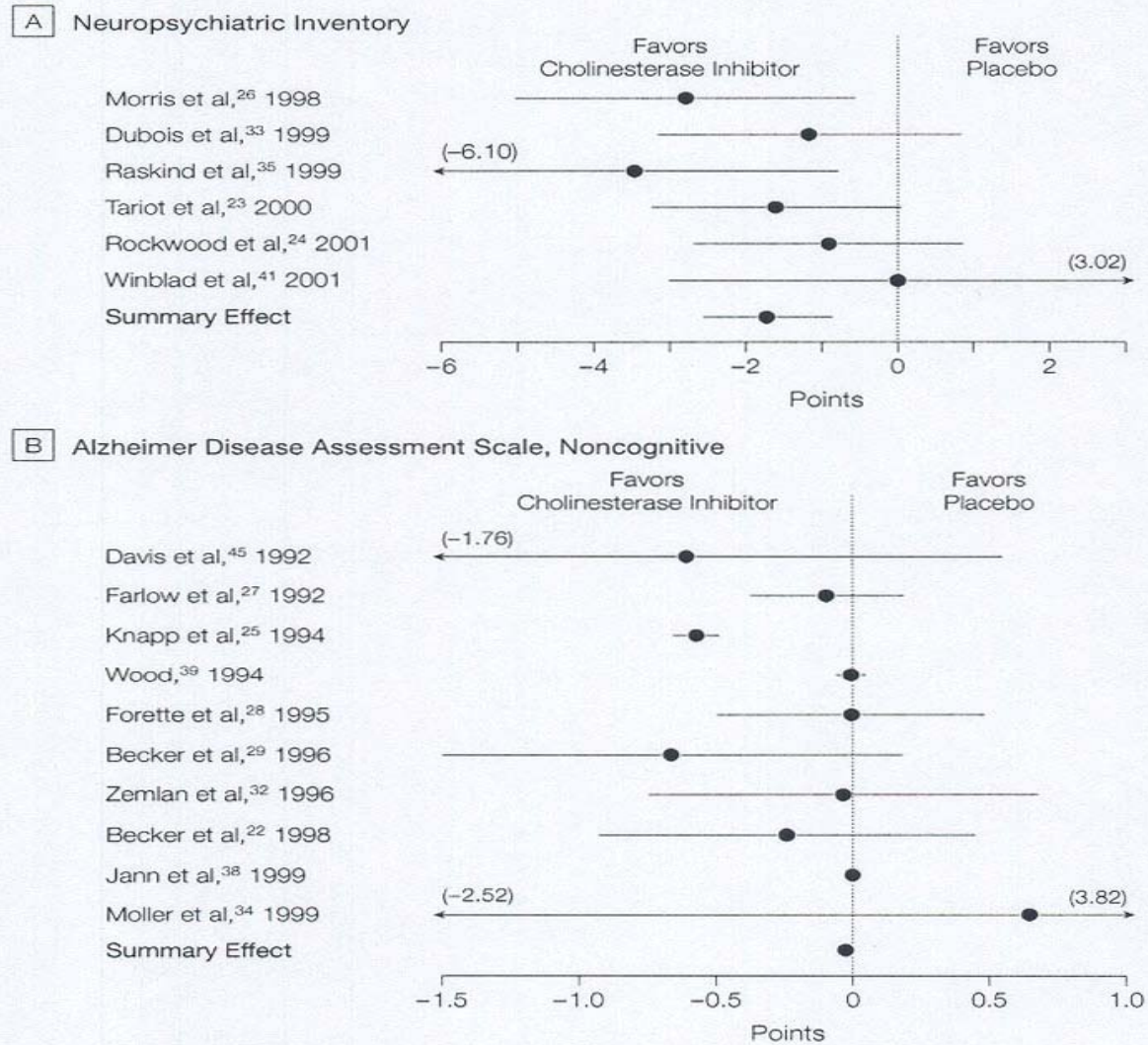
Do cholinesterase inhibitors (CI) reduce depression?

- Meta-analysis indicated that treatment with CI decreased behavioral symptoms (Trinh et al, 2003)
 - 16 studies
 - 10 show CI > placebo and 1 show placebo > CI
- Modest effect overall
- Upshot:
 - Depression may improve with CI treatment.
 - Consider CI as first line for mild depression.
 - For moderate to severe depression use more proven treatments

Cognitive enhancers and NPS

- Meta-analysis indicated that treatment with cholinesterase inhibitors (CI) decrease behavioral symptoms (Trinh et al, 2003)
 - 16 studies
 - 10 show CI > placebo and 1 show placebo > CI
- More limited data on Memantine
- Modest improvement overall
- Upshot:
 - NPS may improve with cognitive enhancer treatment.
 - Initiate cognitive enhancer and monitor NPS.
 - NPS should not be primary indication
 - CI may worsen NPS in FTD

Figure 1. Behavioral Symptoms in Alzheimer Disease



Negative scores denote improvement. Error bars indicate 95% confidence intervals.

Trinh et al, JAMA, 2003

To treat or not to treat? A practical approach

Mild <-----**Moderate** -----> **Severe**

Low CR/CG distress	→	High CR/CG distress
Low risk of harm	→	High risk of harm
Low environment impact	→	High disruption
Low impact CR QOL	→	High impact CR QOL

Treatment considerations:

- Mild: monitor or nonpharmacological or drug
- Moderate: drug with or without nonpharmacological, possible referral
- Severe: drug + nonpharmacological, possible referral, in-patient, ECT

Summary

- Depression is common and costly
- Diagnostic approach must be adjusted
- Nonpharmacological and antidepressant drug treatments show promise
- Cholinesterase inhibitor data much less convincing
- Combination of nonpharmacological and drug treatment is best treatment

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