Anxiety and Depression in Neurodegenerative Disorders

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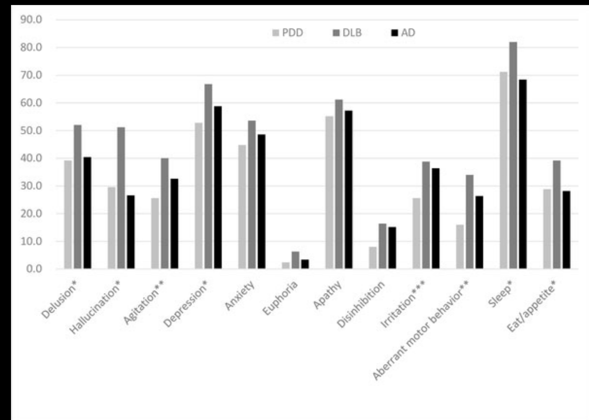
Neuropsychiatric Symptoms of Dementia

- Neurodegenerative diseases are complex disorders that affect multiple brain systems producing a wide range of cognitive and psychiatric symptoms
- More research and focus is spent on cognitive features
- Psychiatric features may be more important for patients and their families

Neuropsychiatric Symptoms

- Psychiatric or behavioral symptoms that emerge in the context of neurological disease
  - 80-90% of patients with Alzheimer's disease will experience some neuropsychiatric symptoms
  - Behavioral symptoms are required for diagnosis of Frontotemporal Dementia
  - Supportive clinical features of Dementia with Lewy Bodies
- Not necessarily the same neurobiology as idiopathic psychiatric disorders; often treated that way="therapeutic metaphor"



Neuropsychiatric Features are Important

- Primary determinant of
  - Where a patient resides (home or care facility)
  - Cost of their care
- Important for differential diagnosis
- Amenable to pharmacological and non-pharmacological intervention
  - One of the few areas that clinician can have significant impact on care for patients with dementia

Impact of Neuropsychiatric Features

- Immense impact that may exceed cognitive features
- Many patients with AD dementia do not remember that they don't remember or be unbothered by their symptoms
- On the other hand,
  - Patients with delusions: tormented by belief they are victims of theft
  - Agitated patients: irritated and uncomfortable
  - Compulsive patients: stressed and anxious

Patients with Neuropsychiatric Symptoms

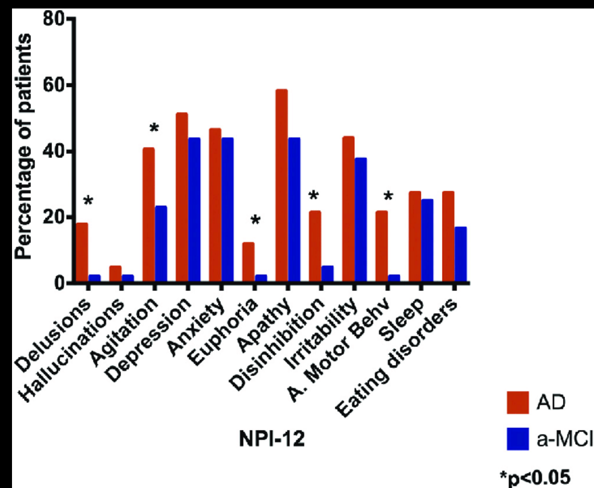
- More likely to be:
  - Engaged in physical altercations
  - Victims of elder abuse
  - Be on pharmacological therapy
    - Psychotropic medications increase mortality, the risk of falls, cardiac abnormalities, and cerebrovascular events

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Studies with various medicines of the group to which ZYPREXA belongs, including ZYPREXA, when used in elderly patients with dementia have been associated with an increased rate of death. ZYPREXA is not indicated in elderly patients with dementia.

Features of Neuropsychiatric Symptoms

-emerge at any stage of disease
-change over time
-symptoms that may worsen:
    agitation
    apathy
-symptoms that may come and go:
    delusions/hallucinations
    depression



Symptom Clusters in NPS

Using Neuropsychiatric Inventory on 5,092 patients with dementia:
    four latent classes of symptoms:
        affective (28%)
        psychotic (13%)
        mono-symptomatic (19%)
        no symptoms (40%)

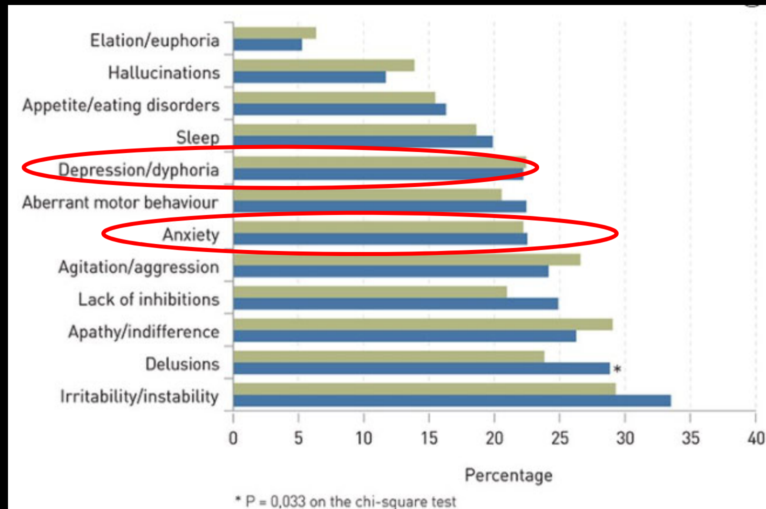
Table 1. Results of previous factor analytic studies using the NPI

Authors	Patients	Mean MMSE score	NPI items	Factors
Frisoni et al. [7], 1999	162	13.3	10	mood/frontal/psychosis
Fuh et al. [16], 2001	95	12.7	12	mood-psychosis/psychomotor regulation/social engagement
Aalten et al. [1], 2003	199	18.1	12	mood-apathy/psychosis/hyperactivity
Spalletta et al. [17], 2004	244	17.5	10	mood-excitement/mood-depression-apathy/psychosis/hyperactivity/anxiety
Benoit et al. [6], 2003	244	23.4	10	psychosis-agitation/mood/hallucination
Mirakhur et al. [13], 2004	435	13.0	12	affect/physical/psychosis/hypomania
Matsui et al. [18], 2006	140	20.3	10	mood/psychosis/euphoria

NPI = Neuropsychiatric Inventory; MMSE = Mini Mental State Examination.

Mood/Affect Cluster

- Depression
- Anxiety
- +/- apathy



Depression in AD

- Wide variation in prevalence rates depending on populations studied, instruments used, and informant (caregiver vs. self report)
- Accepted rate=30-50%, much higher than non-demented rate of 1.5%
- Associated with greater caregiver burden, lower quality of life, nursing home placement
- Associated symptoms: psychosis, wandering, aggression

Features

- Similar as MDD but typically less severe
  - Less likely to attempt suicide
  - Few major episodes
- Common symptoms: sleep, worthlessness, and guilt
- Hard to differentiate from apathy and usually co-exists with apathy

Provisional Criteria

- 1) reduction in total symptoms from 5 to 3 and not everyday
- 2) social withdrawal or irritability
- 3) replacement of anhedonia with decreased positive affect and loss of pleasure associated with social activities

DSM-5
Depressed mood†
Markedly diminished interest or pleasure†
Significant weight loss or weight gain
Insomnia or hypersomnia
Psychomotor agitation or retardation
Fatigue or loss of energy
Feelings of worthlessness or excessive or inappropriate guilt
Diminished ability to think or concentrate, or indecisiveness
Recurrent thoughts of death, recurrent suicidal ideation, or a suicide attempt

Assessment Tools

- NIH Provisional Criteria
- Geriatric Depression Scale (GDS)
- Hamilton Depression Rating Scale
- NPI
- Cornell Scale for Depression in Dementia

HAMILTON DEPRESSION RATING SCALE (HAM-D)
(To be administered by a health care professional)

Patient Name ____________________ **Today's Date** __________

The HAM-D is designed to rate the severity of depression in patients. Although it contains 21 areas, calculate the patient's score on the first 17 answers.

☐ 1. DEPRESSED MOOD
(Gloomy attitude, pessimism about the future, feeling of sadness, tendency to weep)
0 = Absent
1 = Sadness, etc.
2 = Occasional weeping
3 = Frequent weeping
4 = Extreme symptoms

☐ 2. FEELINGS OF GUILT
0 = Absent
1 = Self-reproach, feels he/she has let people down
2 = Ideas of guilt
3 = Present illness is a punishment; delusions of guilt
4 = Hallucinations of guilt

☐ 3. SUICIDE
0 = Absent
1 = Feels life is not worth living
2 = Wishes he/she were dead
3 = Suicidal ideas or gestures
4 = Attempts at suicide

☐ 4. INSOMNIA - Initial
(Difficulty in falling asleep)
0 = Absent
1 = Occasional
2 = Frequent

☐ 5. INSOMNIA - Middle
(Complains of being restless and disturbed during the night. Waking during the night.)
0 = Absent
1 = Occasional
2 = Frequent

☐ 6. INSOMNIA - Delayed
(Waking in early hours of the morning and unable to fall asleep again)
0 = Absent
1 = Occasional
2 = Frequent

☐ 7. WORK AND INTERESTS
0 = No difficulty
1 = Feelings of incapacity, listlessness, indecision and vacillation
2 = Loss of interest in hobbies, decreased social activities
3 = Productivity decreased
4 = Unable to work. Stopped working because of present illness only. (Absence from work after treatment or recovery may rate a lower score).

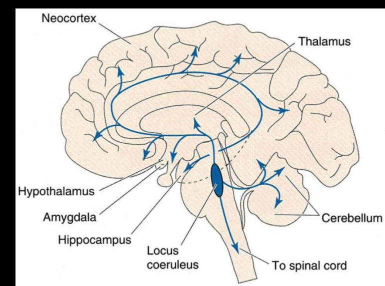
☐ 8. RETARDATION
(Slowness of thought, speech, and activity; apathy; stupor.)
0 = Absent
1 = Slight retardation at interview
2 = Obvious retardation at interview
3 = Interview difficult
4 = Complete stupor

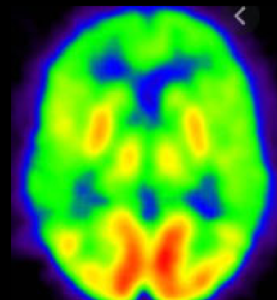
☐ 9. AGITATION
(Restlessness associated with anxiety.)
0 = Absent
1 = Occasional
2 = Frequent

☐ 10. ANXIETY - PSYCHIC
0 = No difficulty
1 = Tension and irritability
2 = Worrying about minor matters
3 = Apprehensive attitude
4 = Fears

Pathophysiology

- Focus on ascending monoaminergic systems
- Areas of increased neuropathology in individuals with depression and AD in key brain areas
  - Locus coeruleus (noradrenergic)
  - Raphe nucleus (serotonin)
  - Substantia nigra (dopamine)
- Lower cortical norepinephrine, serotonin, and CTRH in CSF
- Functional studies=frontal regions (atrophy, metabolism, functional disconnection)



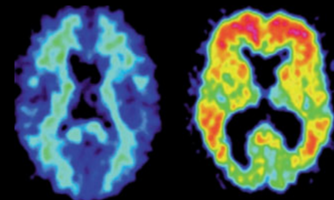


Treatment Recommendations

- Period of watchful waiting for mild cases
- Treatment initiated with severe depression, suicidality, or when depressive symptoms cluster with other NPS to create high risk
- SSRIs as first line
  - 30-50% of AD patients are prescribed antidepressants
- Limited evidence of benefit
  - Meta-analysis fail to find benefit
  - RCTs (sertraline/mirtazapine)=negative
- Best practices=sertraline/escitalopram/citalopram>>>fluoxetine/paroxetine due to fewer anticholinergic effects

Treatment Studies

- Mixed results from SSRIs and Mirtazapine
  - Smaller studies have shown benefit, larger studies have generally failed to find separation from placebo
  - Participants on treatment have higher rates of side effects
- Meta-analyses fail to report benefit

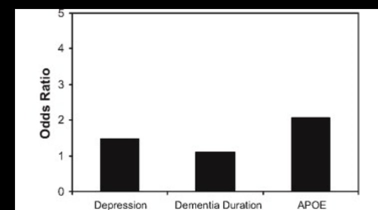


Treatment Recommendations

- American Psychiatric Association recommends treatment of depression in AD: serious symptoms, persistent, danger
- SSRIs as first line
  - 30-50% of AD patients are already prescribed antidepressants
  - Citalopram/escitalopram/sertraline>>>>fluoxetine/paroxetine
- SNRIs and mixed agents are second line
- SSRI added to atypical antipsychotic for concurrent agitation
- ECT for refractory depression

Depression and Risk for AD

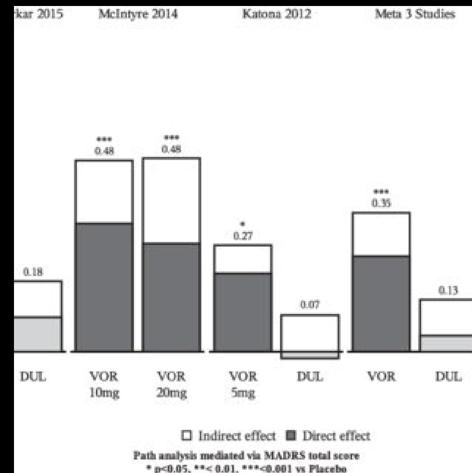
- Number of episodes and number of symptoms has been associated with increased risk of developing AD
- Early life depressive episodes associated with risk of AD
- Metaanalysis: Lifetime episode of MDD 2x risk for developing dementia
- Neurobiological link



Note: Within patients with Alzheimer disease, the presence of depression increased the odds for advanced neuropathologic disease. Braak staging < V versus V and VI; (odds ratio: 1.47, 95% confidence interval: 1.03–2.08, Wald = 4.51, df = 1, p = 0.03). The odds were comparable to dementia duration (odds ratio: 1.09, 95% confidence interval: 1.05–1.12, Wald = 36.40, df = 1, p <0.001), but lower than the risk conveyed by APOE allele status (odds ratio: 2.05, 95% confidence interval: 1.62–2.58, Wald = 29.15, df = 1, p <0.001).

Vortioxetine

- Multiple factors at serotonin receptors
  - Inhibits 5HT transporter
  - Agonist 5HT1A, 5HT1B
  - Antagonist 5HT3, 5HT7, 5HT1D
- Benefit on digit symbol substitution independent of effect on mood

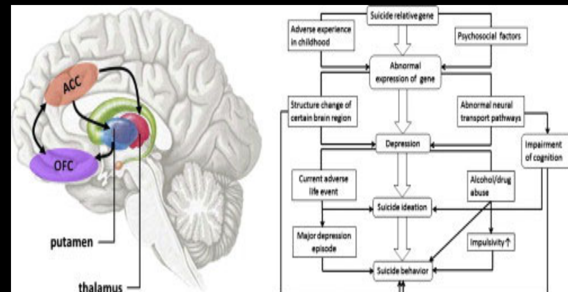


Depression in PD

- Up to 50% of PD patients experience depression
- Minor episodes (10-30%) are more common than major (5-10%)
- Risk=
  - female,
  - personal or family history,
  - psychiatric comorbidity,
  - rigid-akinetic,
  - atypical parkinsonism
- Common in off state, frequency of anxiety or depression in motor fluctuations is 35%
- Levodopa may attenuate mood fluctuation in off state

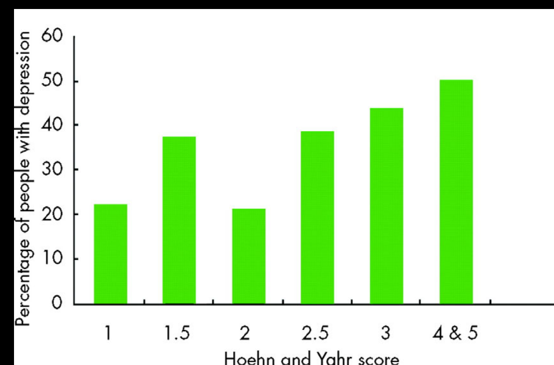
Pathophysiology

- Neural circuits involving the prefrontal cortex and basal ganglia as well as ascending monoaminergic systems



Pathophysiology

- Psychological factors-PD patients more aware, strong associations between depression and disease related functional impairment

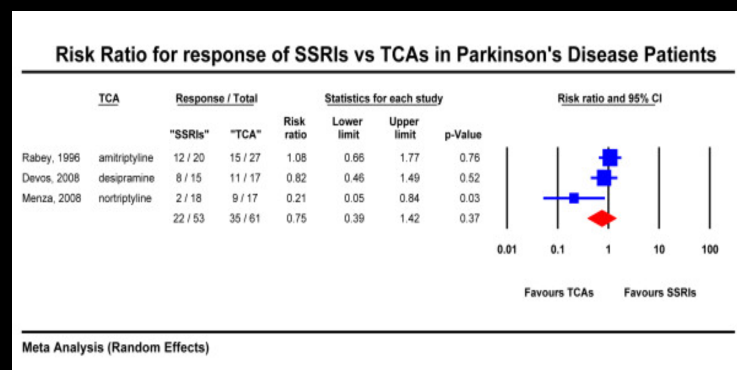


Treatment-PD Depression

- Dopamine agents as first step
  - Pramipexole (0.3-4.2 mg/d)
  - Ropinirole (10 mg/d)
  - Close monitoring for ICD symptoms

Treatment-PD Depression

- If contraindicated
  - Tricyclics are first step if no cognitive impairment
    - Amitriptyline
    - Desiprimine
    - Imopramine
    - Nortriptyline
  - Desiprimine/imipramine may improve motor symptoms



Risk Ratio for response of SSRIs vs TCAs in Parkinson's Disease Patients

	TCA	Response / Total		Statistics for each study			
		"SSRIs"	"TCA"	Risk ratio	Lower limit	Upper limit	p-Value
Rabey, 1996	amitriptyline	12 / 20	15 / 27	1.08	0.66	1.77	0.76
Devos, 2008	desipramine	8 / 15	11 / 17	0.82	0.46	1.49	0.52
Menza, 2008	nortriptyline	2 / 18	9 / 17	0.21	0.05	0.84	0.03
		22 / 53	35 / 61	0.75	0.39	1.42	0.37

Meta Analysis (Random Effects)

Treatment-PD Depression

- If cognitive impairment, consider SSRI
  - Sertraline/citalopram have efficacy data and fewer anticholinergic effects
- Data for SNRIs duloxetine and venlafaxine
  - Less tolerated than SSRIs
- Mirtazapine 30 mg (improvement for dyskinesia)
- Some open label data for selegiline (lack of progression in mild depression)

Treatment-PD Depression

- Treatment resistant, severe depression=ECT
- Psychosis
- Limited cognitive symptoms
- May improve motor symptoms

Conclusion

- NPS dementia are common and disabling
- May respond to pharmaceutical intervention
- In AD, depression is common but less likely to respond to treatment than depression in PD