Neuropsychiatric Symptoms in Dementia: A Case Based Discussion

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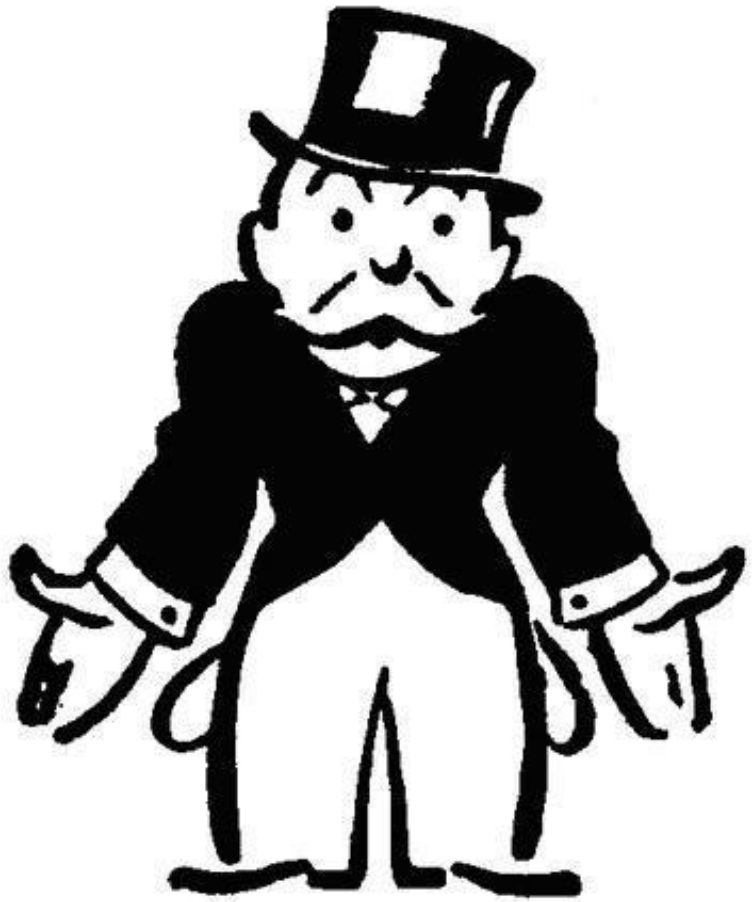
Disclosures

I have no financial conflicts of interest to disclose.



CME Learning Objectives

1. Recognize non-cognitive and non-motor neuropsychiatric symptoms in neurodegenerative disorders
2. Distinguish different neuropsychiatric symptoms in dementia and have a basic understanding on how to use an etiological lens to diagnose and treat
3. Confidently promote behavioral interventions as the first-line of treatment for neuropsychiatric symptoms in dementia.
4. Enumerate the risks and benefits of different pharmacological approaches to neuropsychiatric symptoms in dementia
5. Increase competence in recommending psycho-interventional services (ECT/TMS) for severe and treatment refractory neuropsychiatric symptoms

Dementia is a psychiatric disease.

Memory Loss

Motor Dysfunction

Hallucination

Inattention

Aggression

Anxiety

Apathy

Dysphoria

Autonomic Dysfunction

Tremor

Capgras-type delusions

Inappropriate laughter

Language Deficits

Executive Dysfunction

Agitation

Impulsivity

Change in Personality

Emotional Lability

Sleep Disturbance

Compulsions

Delusions

Wandering

Appetite Changes

Case 1

74yo woman with history of hyperlipidemia and osteoporosis presents with memory decline and attention issues. Family endorsed patient had short-term memory issues going back at least 5 years prior to initial presentation, and she endorses some organizational issues going back 10 years. In addition, she has issues with sequencing and executive function. Initial MOCA 15/30. While she had a fall with head injury around the time of initial cognitive deficits, the subsequent MRI showed multiple microhemorrhages consistent with CAA as well as severe white matter hyperintensities and diffuse atrophy with a focus at the hippocampus. Her cognitive profile suggested frontosubcortical deficits consistent with mixed dementia (Alzheimer's + Vascular Dementia + CAA).

Her mood and personality were noted to be different from her pre-decline baseline, with increased anxiety and rumination as well as increased irritability. There have been some delusions and increases in her demands for attention. Husband noted that her temper has been worse, "frightening" at times. He notes she now tends to rock back and forth while watching TV but otherwise no motor deficits.

Over time, her behavior started to become more challenging, with refusal of care, verbal but not physical abuse, disrobing, and wandering. She has also been concerned about people being in the house when no one else is there. She voiced delusions of episodes of physical harm from caregivers that were not substantiated. She also has appeared hypervigilant at times and can overreact to small stimuli, like light touch. Angry responses to small stimuli are common. These behaviors happen predominantly during the day and are more uncommon at night. There have also been occasional falls.

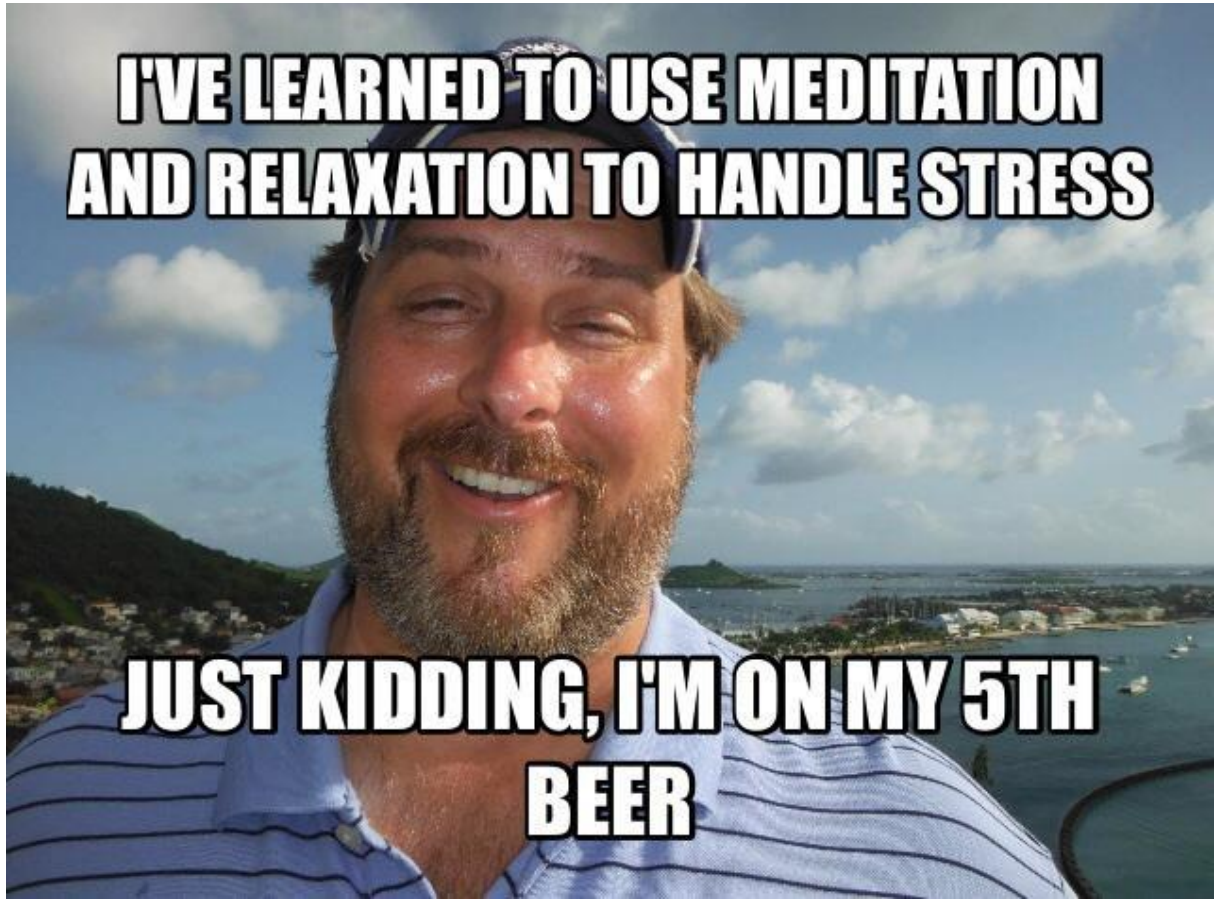
APA Clinical Practice Guidelines 2016:

1) Assess the patient's symptoms
   a) Timing, severity, frequency
   b) Determine if there are other modifiable risk factors, <u>especially pain</u>, that can be addressed
      a) 85% of dementia patients experience substantial pain
      b) American Geriatric Society protocol suggests acetaminophen -> oral morphine -> buprenorphine patch (limited RCTs supporting this) for BPSD/NPS analgesics
2) Begin with non-pharmacological management first and develop a comprehensive treatment plan
3) Non-emergency antipsychotics should only be enacted
   a) For severe symptoms that are dangerous and cause significant distress to the patient
   b) After talking about the risks and benefits with patient and caregiver
   c) Start at low dose and titrate to minimum effective dose
   d) If no benefit within 4 weeks, taper and withdraw
   e) If benefit is shown, an attempt to withdraw and taper should be done at 4 months
   f) During taper, patients should be seen monthly and at least within 4 months of discontinuation

Reus 2016, Tampi 2017

Summary of Specific Behavioral Techniques

- 4 Meta-analyses
- Likely Effective
  - Education and skills for community caregivers
  - Massage/Touch and Music therapy
  - Exercise and outdoor activities
  - Animal-assisted and pet-robot interventions
  - **<u>Person-centered tended to outperform standardized interventions</u>**
- Not shown to be effective…yet (can be issues with power to detect difference)
  - Aromatherapy
  - Light therapy
  - Mindfulness for caregivers
  - Dyadic interventions
  - Reminiscence therapy
  - Reality Orientation Therapy
- One study revealed that in comparison to 71% of elderly nursing home residents who received pharmacotherapy, **only 12% received non-pharmacological treatment**



Keszycki 2019, Tampi 2022

The DICE Approach

Describe

- Caregiver **describes** problematic behavior
  - Context (who, what, when and where)
  - Social and physical environment
  - Patient perspective
  - Degree of distress to patient and caregiver

Investigate

- Provider **investigates** possible causes of problem behavior
  - Patient
    - Medication side effects
    - Pain
    - Functional limitations
    - Medical conditions
    - Psychiatric comorbidity
    - Severity of cognitive impairment, executive dysfunction
    - Poor sleep hygiene
    - Sensory changes
    - Fear, sense of loss of control, boredom
  - Caregiver effects/expectations
  - Social and physical environment
  - Cultural factors

Create

- Provider, caregiver and team **collaborate to create** and implement treatment plan
  - Respond to physical problems
  - Strategize behavioral interventions
    - Providing caregiver education and support
    - Enhancing communication with the patient
    - Creating meaningful activities for the patient
    - Simplifying tasks
    - Ensuring the environment is safe
    - Increasing or decreasing stimulation in the environment

Evaluate

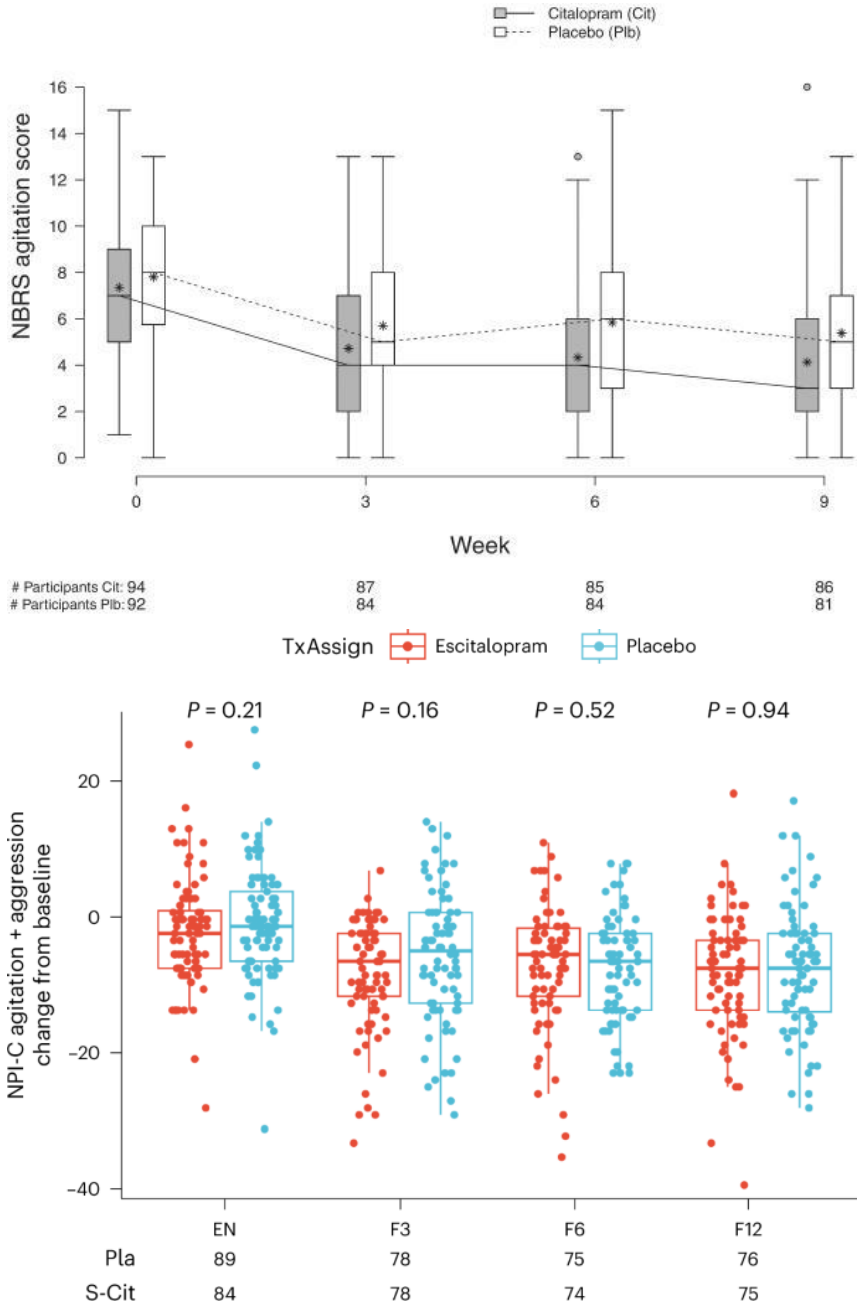
- Provider **evaluates** whether "CREATE" interventions have been implemented by caregiver and are safe and effective

Consideration of Psychotropic Use (Acuity/Safety)

Kales 2014

Antidepressants

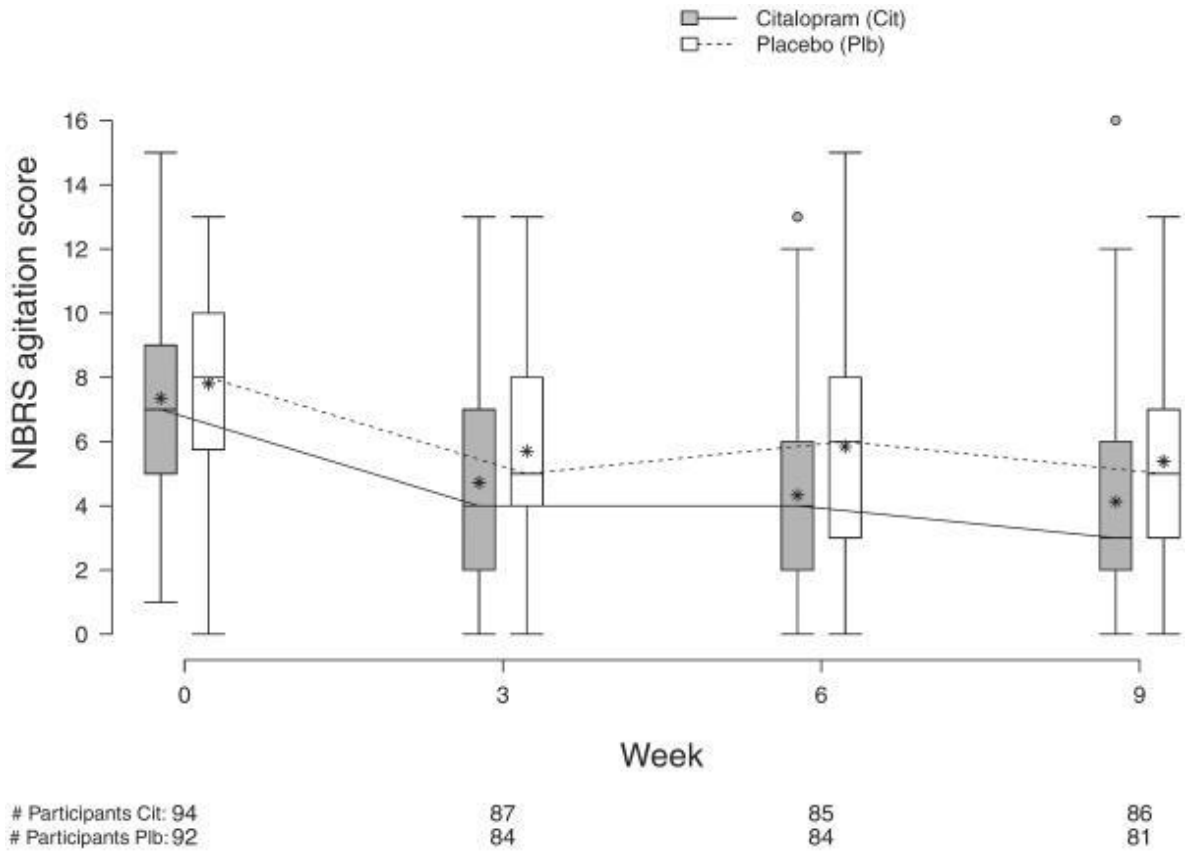
- Canonically, poor for depression treatment in AD
- Prescribed 25-42% AD patients
- CIT-AD:
  - Received brief psychosocial intervention in placebo and citalopram groups
  - Citalopram reduced behavioral symptoms including agitation, irritability, anxiety, delusions, and hallucinations
  - But dose 30mg (QTc)
- S-CIT-AD:
  - Interrupted by Covid and c/b lots of baseline citalopram use, so under-recruited
  - Pt were FIRST give brief psychosocial intervention, and if responded, were ineligible
  - No statistically significant differences, but:
    - 12wk moderate/marked improvement: 34.5% vs 27%, p = 0.31
  - Percentage of pt with higher QTc greater in escitalopram group



Sultzer 1997, Teri 2000, Lebert 2004, Seitz 2011, Porsteinsson 2014, Leonpacher 2016, Farina 2017, Banerjee 2023, Chen 2023, Rajji 2025

Antidepressants

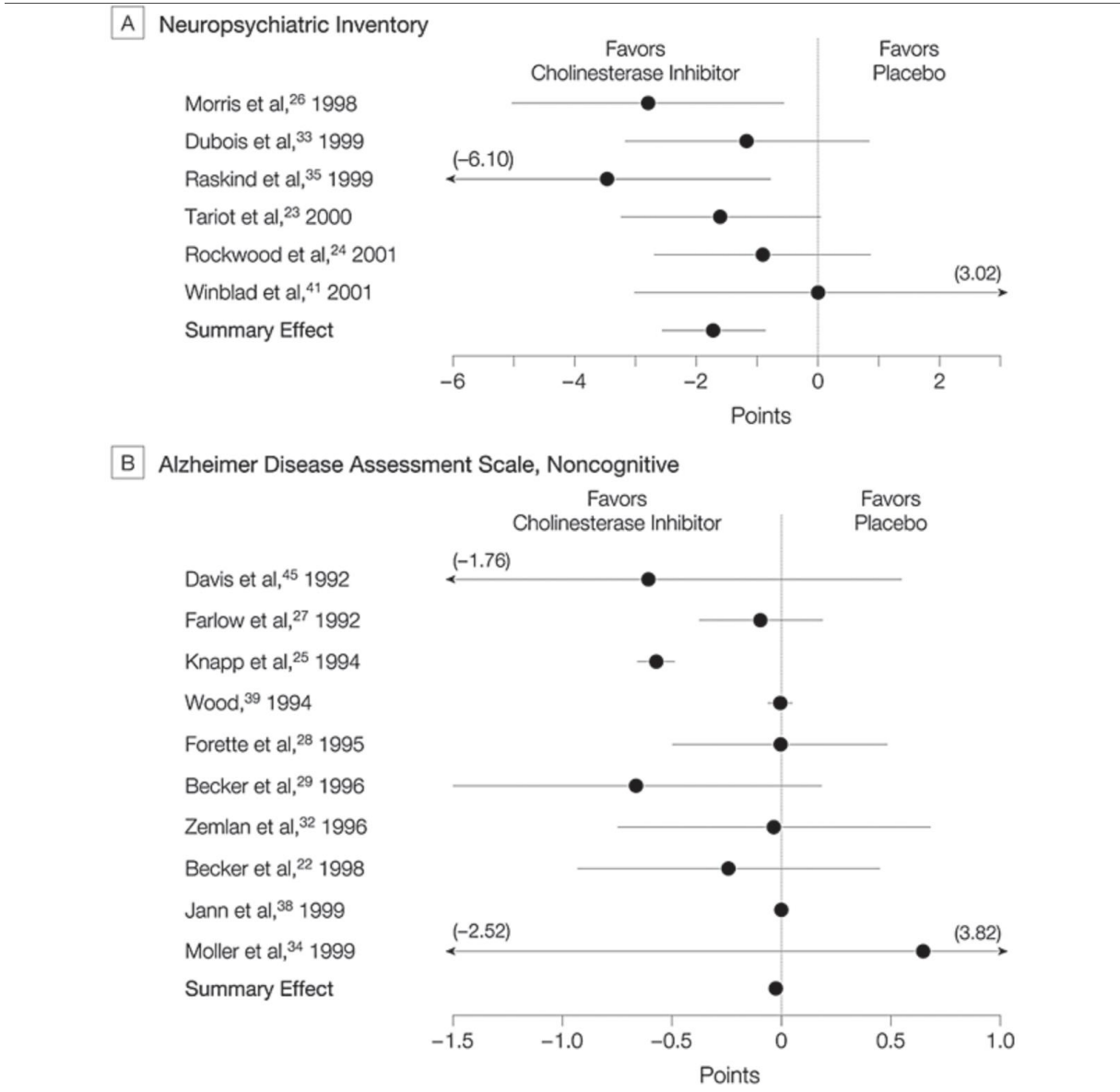
- 2011 Cochrane:
  - Antidepressants likely to be as beneficial as antipsychotics
  - Citalopram and sertraline best evidence
- 2023 Network Meta-Analysis
  - Only citalopram (not sertraline, mirtazapine, or trazodone) effective in reducing agitation
- Trazodone
  - No difference for inpatient agitation compared to Haldol (small RCTs) but also potentially no difference compared to placebo
  - One small positive RCT for FTD related ”BPSD”
- Mirtazapine
  - Moderate Phase III trial (HTA-SYMBAD) found no benefit for agitation and not cost-effective



Sultzer 1997, Teri 2000, Lebert 2004, Seitz 2011, Porsteinsson 2014, Leonpacher 2016, Farina 2017, Banerjee 2023, Chen 2023, Rajji 2025

“Cognitive” Enhancers

- Acetylcholine-esterase inhibitors may be helpful
  - Meta-analysis shows mild improvement on large scale psychiatric assessment
  - No difference between specific agents
- Memantine may be helpful
  - Small improvement on large scale psychiatric assessment
- Most practice guidelines suggest while these medications can reduce NPS, they should only be prescribed as indicated to treat cognitive deficits

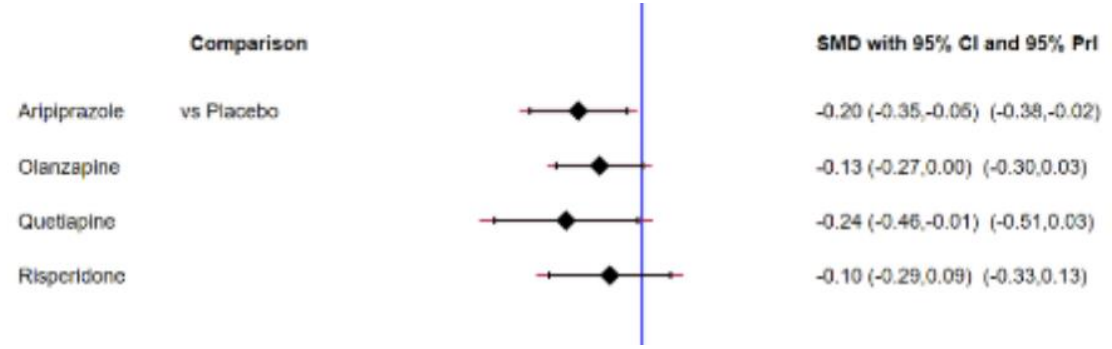


Trinh 2003, Maidment 2008

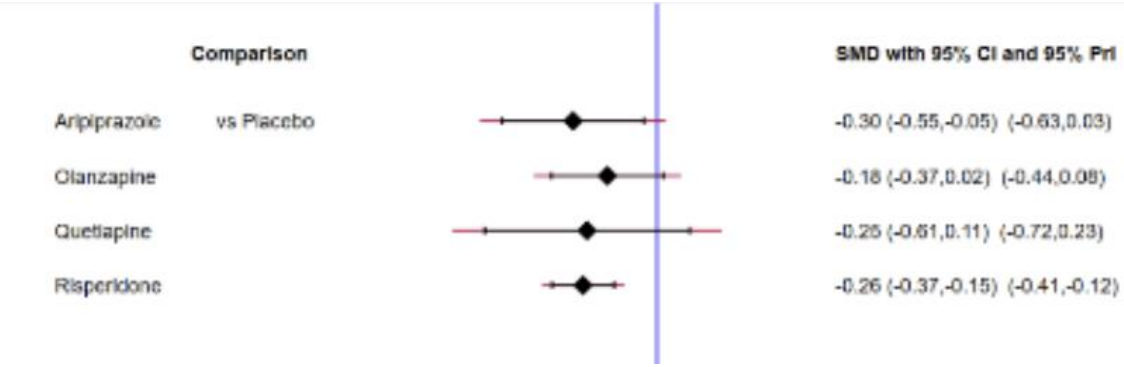
Antipsychotics

- Approved for BPSD in Europe, Canada, New Zealand, Australia
- 2019 Network Meta-analysis:
  - No single APD ultimately outperformed others
  - Aripiprazole most consistently effective compared to placebo
  - Risperidone lowest risk of death
  - Aripiprazole and olanzapine best to reduce CVA
- CATIE-AD (Atypicals)
  - Mortality: NNH 87
  - Stroke with risperidone: NNH 53
  - EPS: NNH 20
  - UTI: NNH 16-36
- BEERS, STOPP, START advise against
- FDA Black box warning for all antipsychotics

BRSD



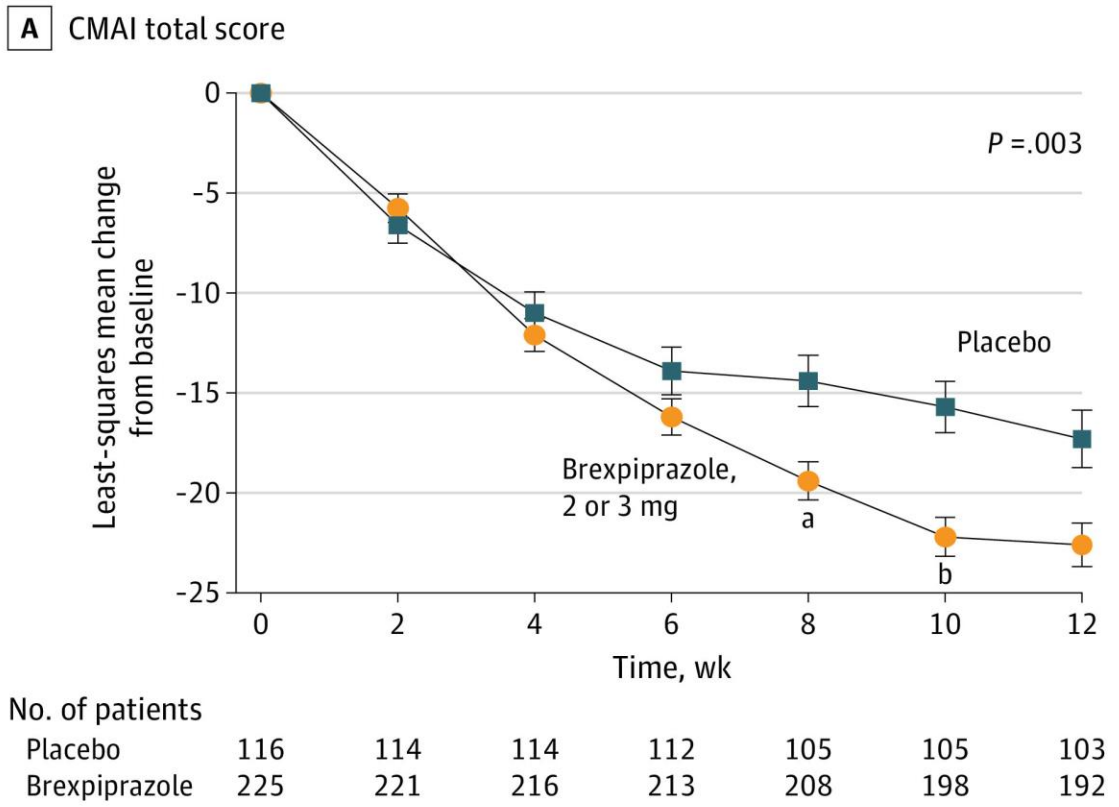
CMAI



Schneider 2006, Reus 2011, Maher 2016, Leeuwen 2018, Yunusa 2019

Antipsychotics

- Pimavanserin: RCT suggested no benefit for agitation/aggression in AD
  - Re-analysis of those with only severe psychosis did suggest some benefit for psychosis but not for agitation/aggression
  - Similarly, while positive effect for psychosis in lewy body disorders, no clear it reduces agitation/aggression
- Brexpiprazole FDA approved for agitation in dementia
  - Unclear how it differs significantly from aripiprazole
- 2016 Cochrane: Discontinuing APD may decrease mild (but not moderate or severe) agitation



Cummings 2014, Kitten 2018, Ballard 2018, Yunusa 2019, Lee 2023

Case 1 - Continued

Initially, the patient was trialed on sertraline for anxiety, but this was discontinued due to diarrhea. She was switched to lexapro 10mg. Her primary care physician had prescribed quetiapine 12.5mg qAM + 25mg qHS, but this just led to drowsiness without change in behaviors. Her neurologist switched her to risperidone 0.5mg BID + risperidone 0.5mg PRN. Ativan was added 0.5mg PRN for aggression, and while used sparingly, daily occurrences of agitation persisted.

With initial pharmacology unsuccessful in preventing agitated events, a psychiatrist was consulted. On interview, the patient expressed that one of her caregivers had thrown her down the stairs and so she was often fearful – her husband later told the psychiatrist that this was a fixed delusion and did not occur. Despite this, it is true that when that caregiver was left alone with the patient, the patient hit her, and the police needed to be called.

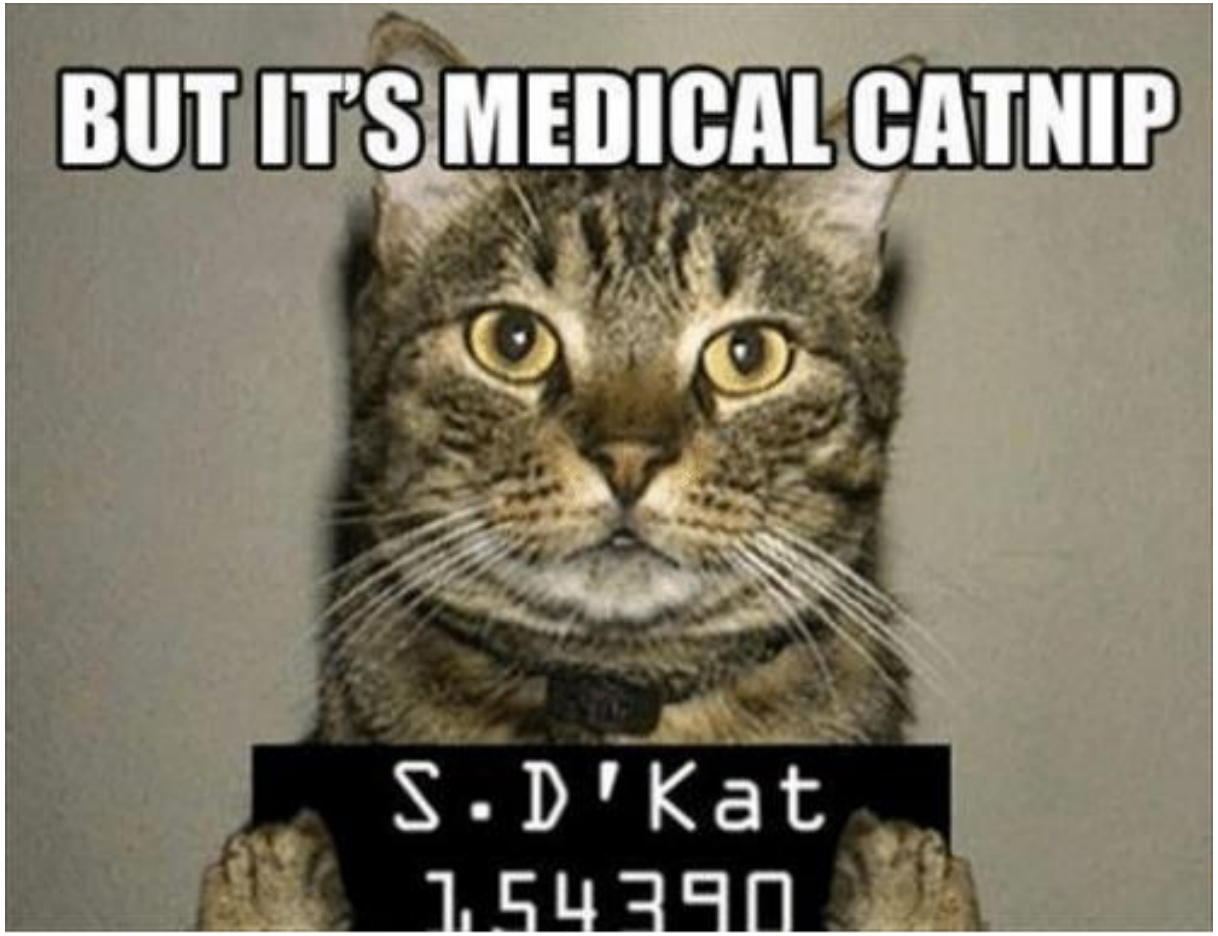
Case 1 - Continued

However, the patient noted she felt very safe with another caregiver, saying the caregiver "constantly puts me at ease.... I'm at ease with her." Her husband agreed and noted that the caregiver often encourages physical activity, including walks outside and yoga. He also notes that the caregiver stays calm, often using a quiet voice and redirection successfully.

During the interview, the husband accidentally put his hand on the patient’s hand as he was getting up, and she yelled out that it had really hurt, physically lashing out at her husband – though brief. It was apparent that the husband had lightly brushed her hand. He noted that she is particularly frightened with loud noises, and she is "on edge."

Anti-epileptics and Mood Stabilizers

- 2018 Cochrane for Depakote: likely ineffective
- Lithium (Lit-AD)
  - No benefit in small-moderate sized RCT
  - Though may be underpowered for smaller effect sizes or in efficacy in subpopulations (more mania-like presentations)
- Cohort, small RCTs, or case studies
  - Gabapentin: Small benefit, no RCT
  - Lamotrigine: Small benefit, no RCT
  - Topiramate: Small benefit, small RCT
  - Levetiracetam : Mixed, no RCT
  - Carbamazepine: Mixed, small RCTs
  - Oxcarbazepine: No benefit, RCT



Ballard 2009, Baillon 2018, Gallagher 2018, Keszycki 2019, Devanand 2022

Medications NOS

- Noradrenergic blockers
  - Small trials for prazosin, propranolol, pindolol with some success
  - Larger phase II prazosin trial (not published; PEACE-AD) showed no response but Covid greatly impacted recruitment, so unclear results
- 5-HT1a modifiers
  - Mechanistically, reduced occupancy may be linked with impulsive aggression – however, due to autoreceptor function, hard to draw conclusions
  - Case reports and retrospective study show modest benefit of buspirone
  - 1 small, open-label RCT show modest benefit for tandospirone (partial agonist)

Cummings 2015, Wang 2009, Passmore 2008, Peskind 2005

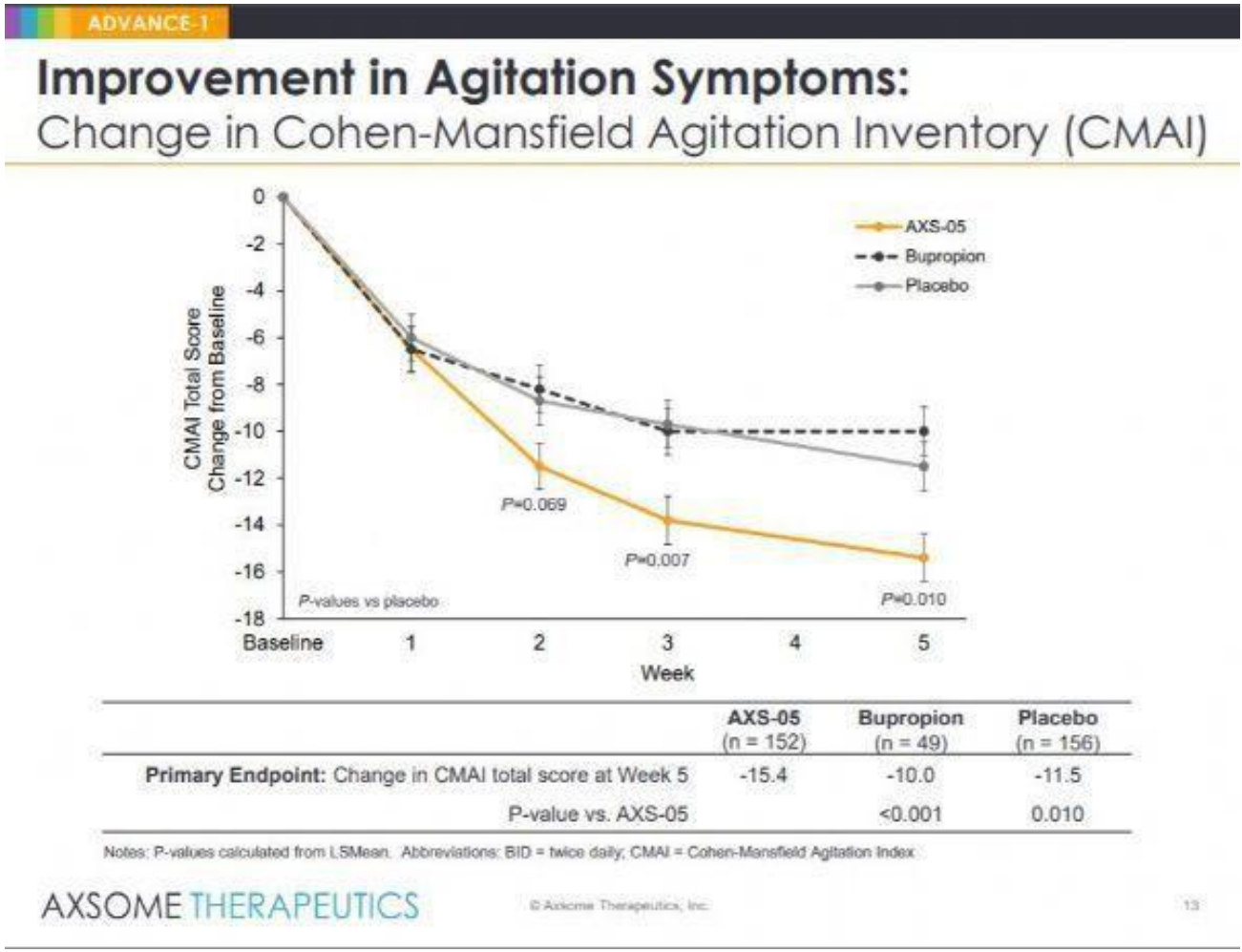
Case 1 - Continued

The psychiatrist decided to trial prazosin, given the patient's strong responses to stimuli, and she gets up to 2mg BID using a dosing schedule of increasing the daily dose by 1mg every 3 days. During this period, she was transferred to an assisted living facility. 6 weeks later, her husband noted that the transition to assisted living had been hard for the patient, but that she is getting better each day. He specifically noticed that she didn't seem to be as on edge or reactive as before. The patient expressed that she was not fearful anymore, but she is adamant that she does not need assisted living. The facility director reports she is often "exit seeking," but he notes she is "very compassionate with other residents." They have used Ativan 4 times in the 10 days since she arrived and have not tried risperidone PRN. The staff suggests increased agitated when her husband leaves after a visit, and they request he not visit for a while. The psychiatrist is uncomfortable with this plan, but instead stresses that behavioral interventions such as validation and focusing on giving patient a sense of purpose could be helpful. In addition, the psychiatrist suggests trying risperidone PRN instead of the Ativan for less acute situations.

Despite a relatively good clinical visit, the patient disrobes and assaults staff two weeks later. The assisted living facility drops her off at the county emergency department and says she is not welcome back.

More Medications NOS

- Dextromethorphan
  - Multiple receptor targets (but mostly NMDA antagonist)
  - Quinidine or Bupropion increases half-life via 2D6 inhibition
  - Approved for pseudobulbar affect in ALS in Europe
  - Recent RCTs showed benefit for agitation/aggression in AD on some but not all trials (ADVANCE-1 and ACCORD tended towards more positive results while TRIAD-1 and 2 tended towards more negative results)



Sherman 2018, Santa Cruz 2017, Sato 2007, Lee 2023

Experimental Medications NOS

- Dexmedetomidine
  - Alpha-2 agonist (Precedex)
  - Frequently used for ventilator-associated agitation in ICU
  - TRANQUILITY phase II RCT (unpublished but press release*) with rapid onset of improvement in agitation
  - May be useful for PRN but unclear use for longer term maintenance
- Cannabinoids
  - RCTs have shown no benefit for THC
  - Small trials and retrospective studies have suggested some benefit for dronabinol, nabilone, and cannabis oil
  - Larger trials for dronabinol and nabilone are ongoing
- Agomelatine (melatonin agonist w/ 5HTc antagonism): Improvement in aggression in small RCT

Lee 2023, Kargar 2025

Case 1 - Continued

The patient was admitted to a geriatric psychiatry unit. They removed all her psychoactive medications and switched her to dextromethorphan 45mg (7.5mL) daily, bupropion 100mg daily, quetiapine 25 - 50mg every hour PRN (requiring about 1 each day), and ativan 0.5-1mg q6hr PO PRN for extreme agitation when quetiapine failed. She was also trialed on depakote without effect. Her meds were crushed to increase adherence.

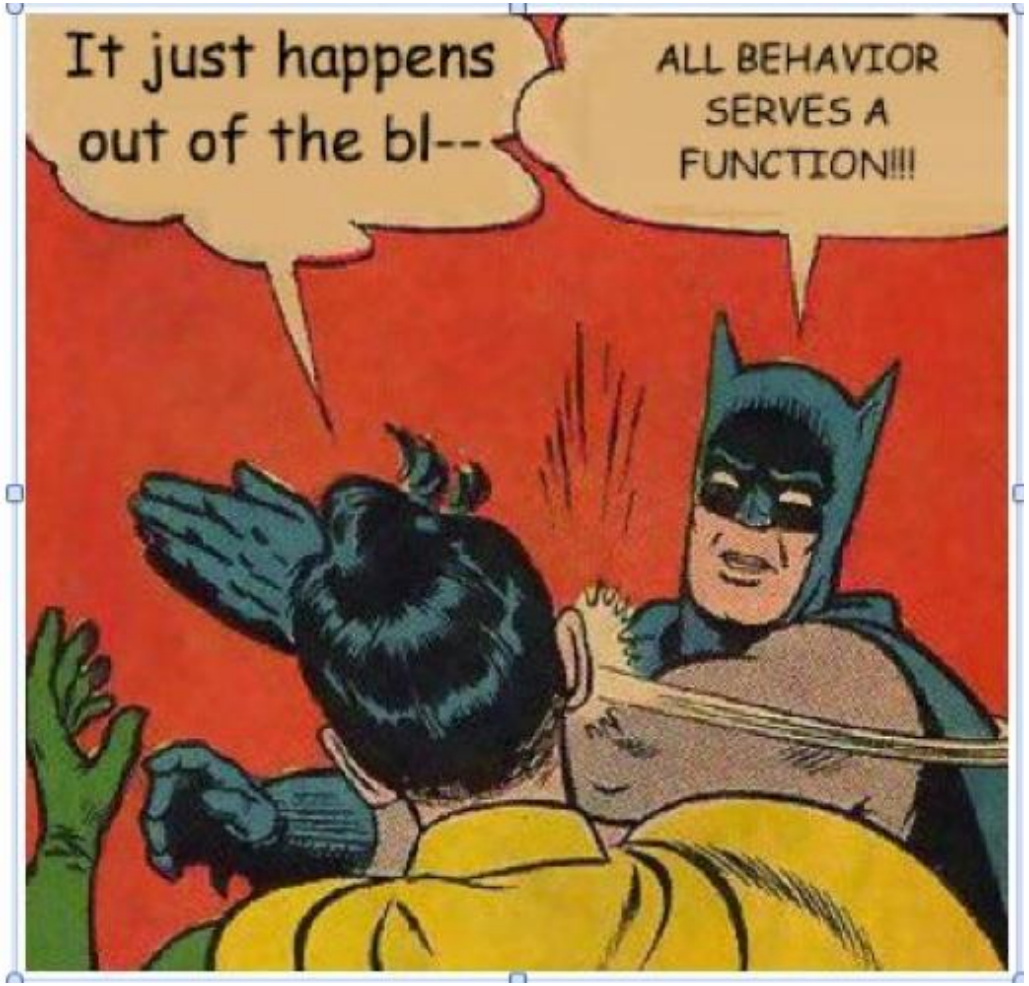
She is discharged to the memory care, who requested more quetiapine from the outpatient psychiatrist soon after receiving the patient, and she is put on quetiapine 25mg TID and 25-50mg QID PRN for breakthrough agitation. Despite this, the memory unit is not satisfied and requests more medication. They recommend increasing the bupropion (not an SSRI), despite the psychiatrist commenting that it is unlikely to improve agitation or anxiety, as its role is to increase the length of dextromethorphan activity and has negligible serotonergic activity. The facility insists, and the psychiatrist is ultimately willing to try BID dosing of bupropion. He reminds the staff that the patient tends to do better with a sense of purpose and encourages them to incorporate some behavioral interventions to increase the patient's sense of belonging and community.

Case 1 - Continued

The patient, family, and director of the memory unit follow-up 6 weeks later. The director says that they have used Ativan almost every day and wants it scheduled. Despite this assertion, the memory unit faxed their MAR, which reflects Ativan use 2-3/week and primarily in a 1-2 week period. When this is noted to the director, they are visibly upset and calls for the charge nurse, who reports the patient has been more sexually promiscuous, disrobing and engaging in sexual activity with multiple new partners. Staff reports she has taken a new boyfriend, though unfortunately that person is at a lower cognitive status and the staff has to remove her. They are concerned for the safety of other residents. They note that there does not tend to be agitation on days when her husband visits, and she generally enjoys speaking with him and her daughters over zoom. It is noted in the MAR that PRNs are always given by two staff members but never from other staff members who work with the patient. Agitation is always noted to be in the afternoon. While the staff request more Ativan and more Seroquel (or “something stronger”), the psychiatrist increases dextromethorphan from daily to BID and restarts Lexapro. Again, the psychiatrist tries to discuss behavioral interventions, but the rest of the team are focused on medications.

Inappropriate Sexual Behaviors

- Prevalence likely between 7-25% of those with dementia
- Evidence for treatment is sparse (cases and case series, often focusing on men)
- 1st line behavioral interventions target 3 areas
  - Environment
  - Behavioral approaches (redirection, distraction, changes in clothes, other methods of stimulation, and engagement to prevent boredom)
  - Psychoeducation of family and staff



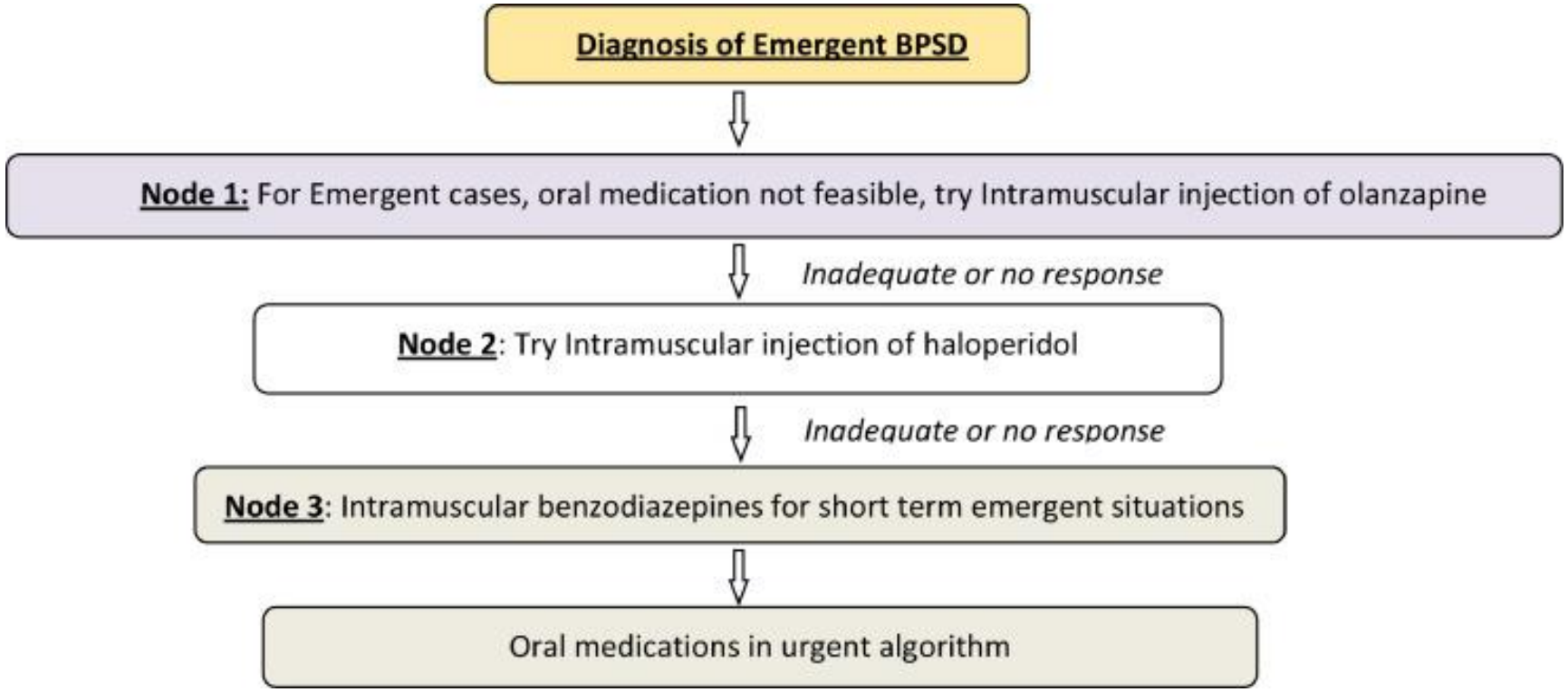
De Giorgi 2016, Sarangi 2021

Inappropriate Sexual Behaviors - Pharmacology

- SSRIs – a number of successful cases and often thought of as first-line pharmacology by experts
- TCAs – only clomipramine with one positive case report
- Antipsychotics – also a few positive case reports for Haldol and Seroquel
- Gabapentin and Carbamazepine have positive case reports while Depakote does not
- Cholinesterase inhibitors – conflicting data
- Anti-androgens – Beneficial but ethically questionable
- Beta-blockers – Some positive case reports in male patients
- Buspar worked for one patient with VaD
- Cimetidine (non-hormonal, anti-androgen properties) – One small study (n = 20) reported improvements in 70% of patients

Di Giorgi 2016, Sarangi 2021

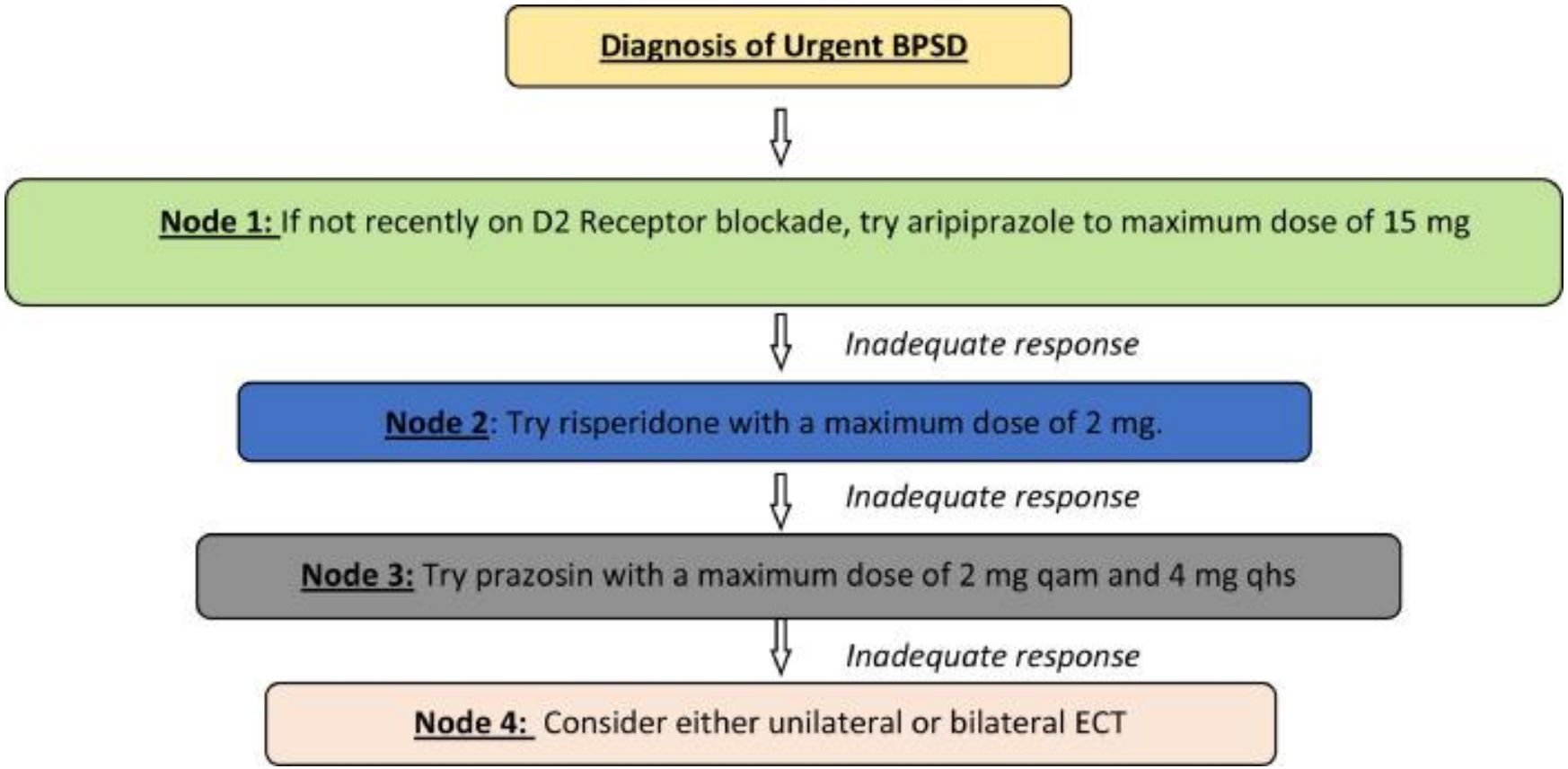
Psychopharmacology Algorithm Project*



*I do NOT professionally endorse this algorithm but believe it is a helpful starting point. I present it as one potential scaffold for clinical management.

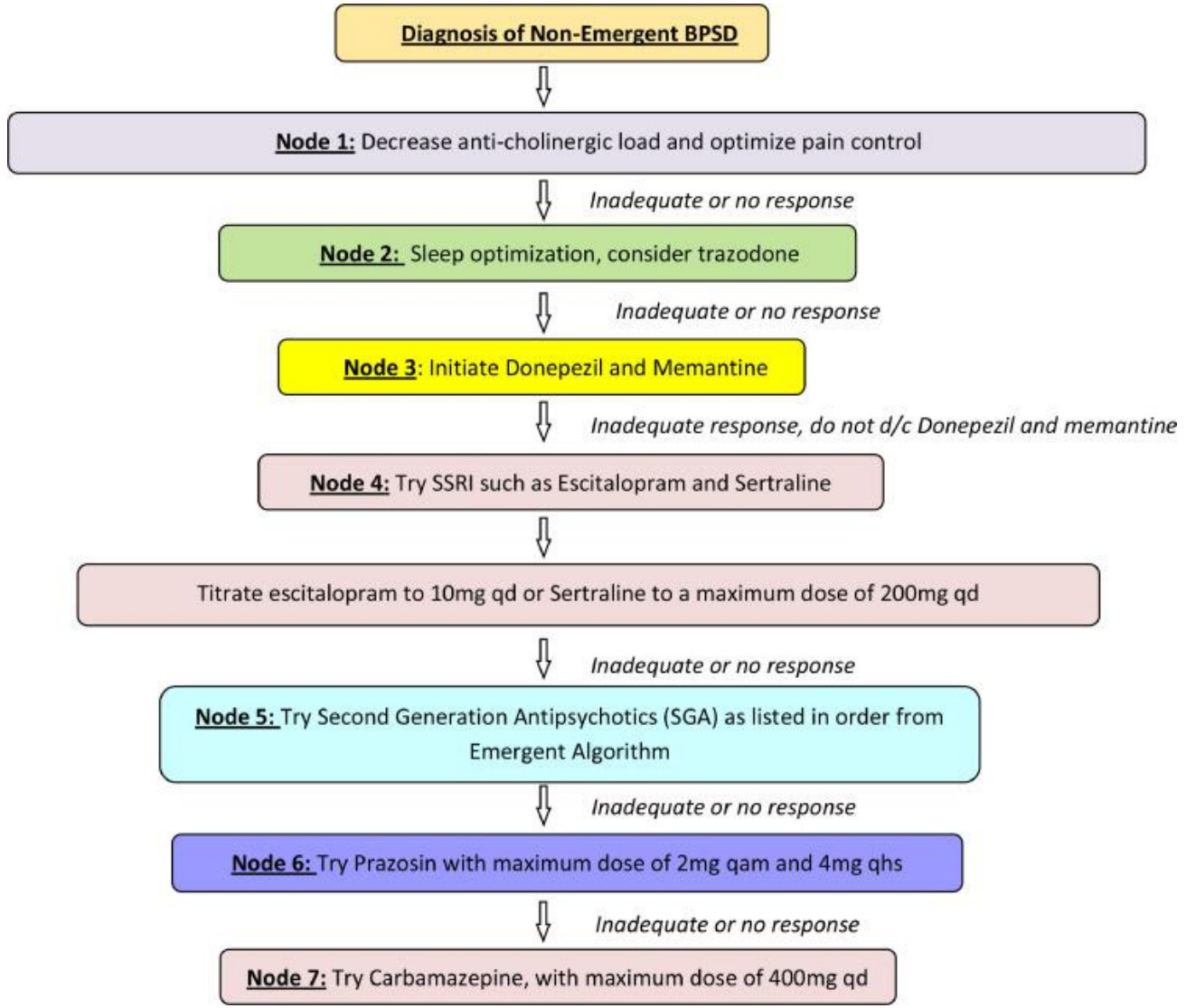
Osser 2013, Chen 2021

Psychopharmacology Algorithm Project



Osser 2013, Chen 2021

Psychopharmacology Algorithm Project



"With exceptions in certain clinical situations described previously, we recommend avoiding the following medications: valproic acid, olanzapine, quetiapine, and benzodiazepines."

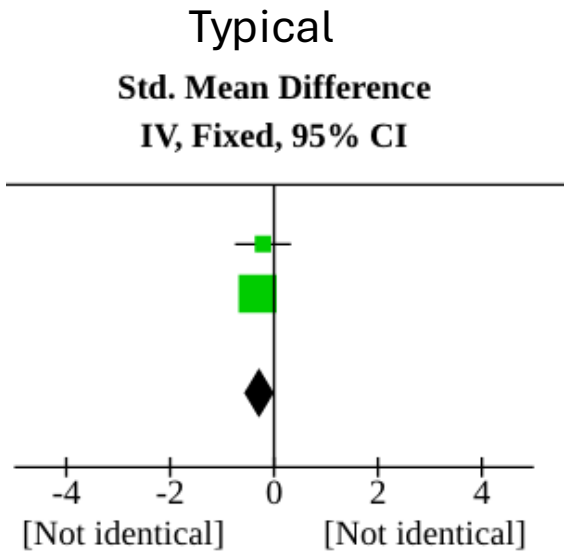
Osser 2013, Chen 2021

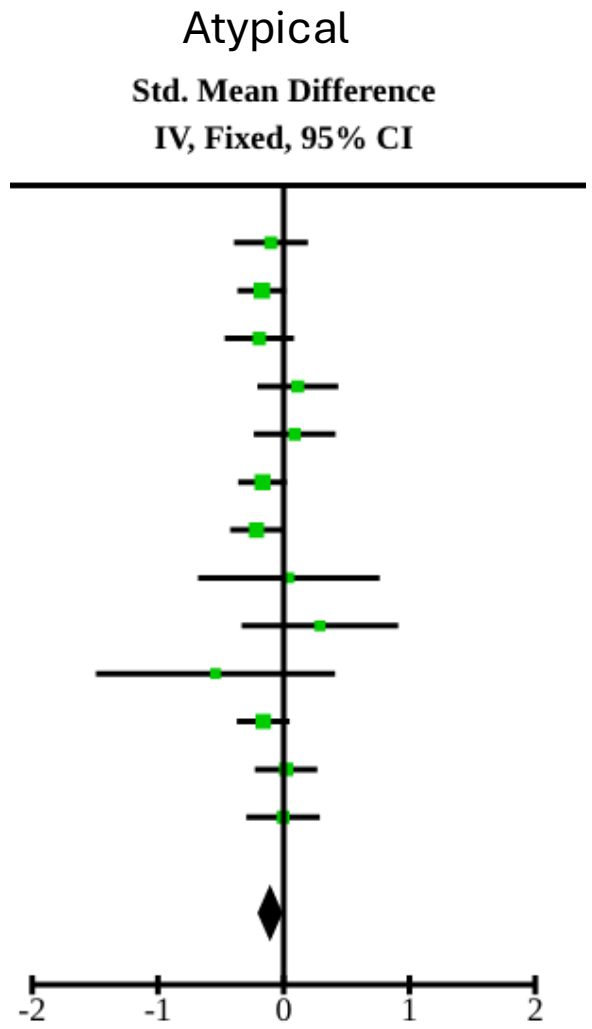
Case 2

55yo F with dementia presents with 1mo of delusions that Harry Potter and Hogwarts are real. Prior to presentation, the patient had a 2-year history of worsening executive function, requiring her daughter to schedule her appointments at work, write her emails, and even perform many of her tasks as an FDA officer. The patient often laughs inappropriately and bursts into song spontaneously (but not in a cool, highschool-musical way). She often lacks empathy and sometimes puts non-food items in her mouth. Her FDG-PET showed significant hypometabolism of the frontal lobes. Husband reports that one morning he found the patient writing letters to Neville Longbottom, Minerva McGonagall, and Luna Lovegood. She expressed concern that her owls are being intercepted by the Dursleys. She hopes that some old shoes in her closet may fit Luna. She is very worried that the children at Hogwarts aren't being treated well. When asked about this, she partially acknowledges that Harry Potter isn't real, but then a second later expresses that she is living under the stairs (there are no stairs in the house). She sometimes looks out the window worriedly, and when her husband asks why, she remarks she heard someone around the house who may hurt her. She says it was someone she saw at the airport recently; the family did just return home from a trip.

Psychosis

- More often visual than auditory hallucinations
- More common with LBD but happen in all dementias
- Cochrane Review
  - Surprisingly, typical antipsychotics may have a small effect but less likely for atypical antipsychotics
- Cit-AD: Secondary analysis showed reduced frequency of delusions and reduced severity of hallucinations on citalopram compared to placebo
- Bottom Line: DO NOT treat with antipsychotic unless hallucinations are distressing, compromise other aspects of care, or put the patient or caregiver in a dangerous situation





Leonpacher 2016, Mühlbauer 2021

Case 3

72yo M history of hypothyroidism, D2M, HTN, prostate cancer (in remission s/p TURP), nephrolithiasis, dysphagia, and dysphonia presents with visual and extracampine hallucinations (feeling of presence when nothing is there). The patient reports that this summer he had episodes where he felt like he was seeing clouds or shapes in his vision. He was not distressed by the hallucinations, but he also began having the feeling like there was a human presence near him when no one was around, which he finds mildly distressing. He also notes snoring while sleeping, and his wife recently moved to a different bed within the last few years. It is not clear if these hallucinations happen around sleep. On exam, he has hypophonia, RUE increased muscle tone, bilateral intermittent tremor, positive pullback test, decreased right arm swing with gait, and a MOCA of 18/30. Family reports that there are times when he seems much more fatigued and with much worse cognition, but that these periods can fluctuate throughout the day. His wife reports years of acting out his dreams, which is why she moved beds, and he has had changes in his gait that precede these symptoms.

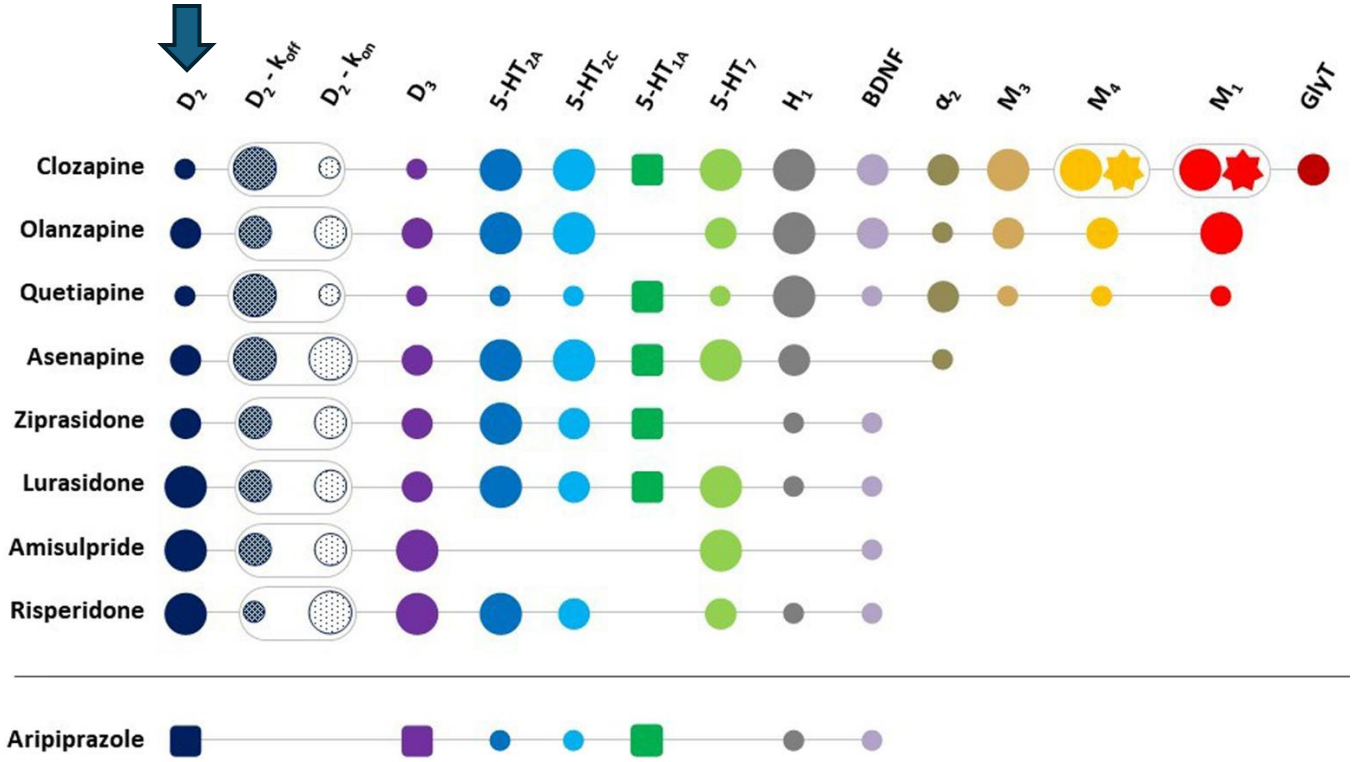
Psychosis in Lewy Body Disorders

- Lewy Body Dementia (LBD) occurs when cognitive symptoms precede motor symptoms or come on within 1 year of motor symptoms
- Parkinson's Disease Dementia (PDD) occurs when motor symptoms present first and dementia does not appear for at least a year
- Up to 80% of LBD and 30% of PD patients with psychosis
- D2R blockade is DANGEROUS
- If rapid onset with recent change in PD medication, consider reversing change
- Most clinical trials are done in PD not LBD
- Cholinesterase inhibitors, especially rivastigmine, may improve psychosis (2 moderate sized RCTs)
  - Whether this extends to other dementias is unclear

Kyle 2020

Psychosis in Lewy Body Disorders - Antipsychotics

- Quetiapine
  - No benefit in PD RCTs, but small trials and with drug dosages <200mg
  - Unclear if *distress* from hallucinations were lower
  - No worsening of motor sx on UPDRS
  - As effective as clozapine in comparator RCTs
- Clozapine
  - Low dose but not high dose clozapine effective for psychosis in PD RCTs
  - Not often used due to severe SE and REMS for prescribing
- Pimavanserin
  - 5HT2a inverse agonist
  - Meta-analysis of 4 RCTs suggests reduction in psychosis but only 1 phase 3 trial
  - Still on patent
- Other antipsychotics can cause worsening of motor function



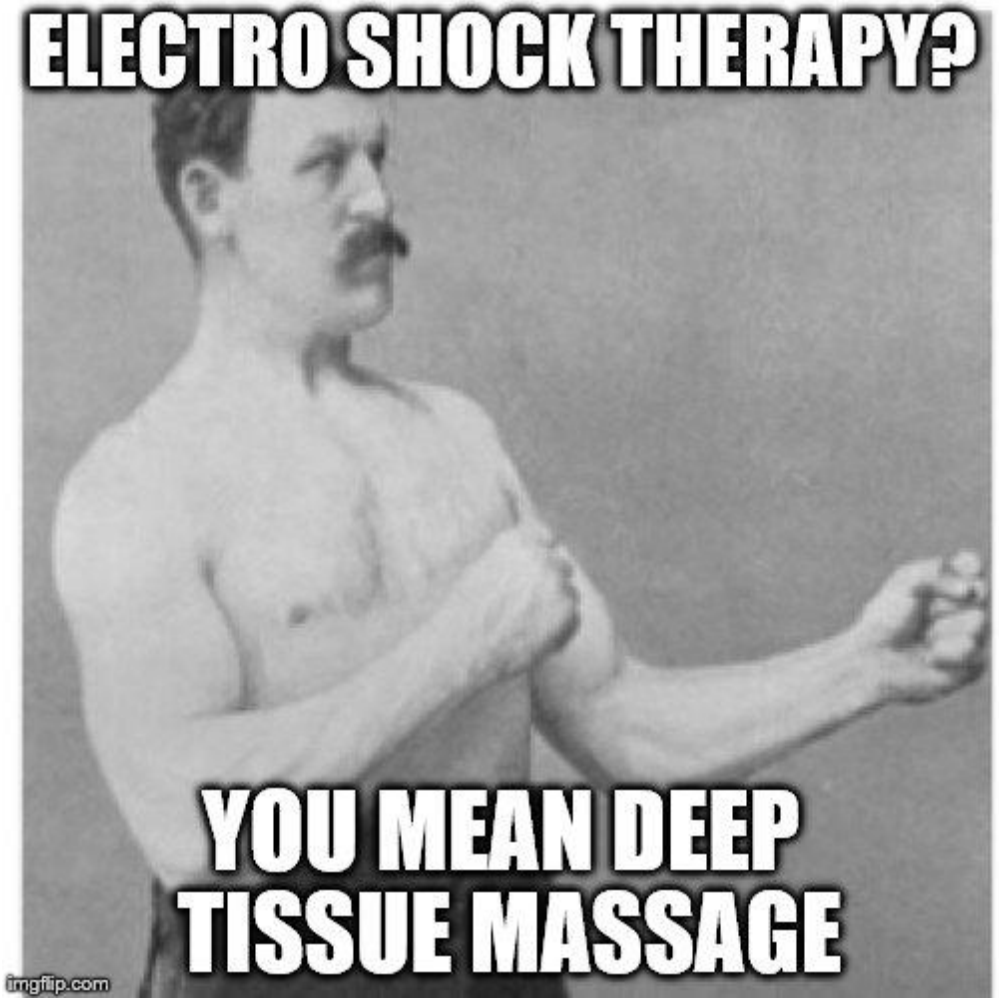
Kyle 2020, Aringhieri 2018

Case 4

73yo F with history of hypertension, hyperlipidemia, hypothyroidism, functional dyspepsia with visceral hypersensitivity, osteoporosis presenting with moderate AD dementia with agitation. The patient started having short term memory loss and mild word-finding difficulties about 4-5 years prior to presentation, and had CSF findings consistent with AD. The patient's family reports she has had high anxiety and abdominal pain that began before her AD diagnosis (onset ~5 years) and has had extensive GI work-up, ultimately concluding 'visceral hypersensitivity'. She wakes up every morning with concerns of abdominal pain that only subside when she goes on walks, which she has to do multiple times a day. She is often very anxious throughout the day, which coincides with her pain bouts. She often refuses to eat during these bouts. Her treatment regimens have included: Nortriptyline, sertraline, duloxetine, escitalopram, Xanax PRN (sparingly), rivastigmine patch, memantine, gabapentin, dicyclomine, amitriptyline, mirtazapine, peppermint tea, ginger tea, carafate, quetiapine, buspirone, and prazosin. While some therapies have led to short-term improvements, no therapy has yielded long-term cessation of symptoms. The patient's husband finds it hard to keep up with patient's demands to walk now that she can no longer do so on her own.

Electroconvulsive Therapy in Dementia

- ECT is safe and *very* effective
- There are no absolute contraindications to ECT
- ECT is safe in dementia
  - Side-effects, mostly post-ictal delirium and cognitive effects, are transient
  - There can be issues with proper consent
- Agitation in dementia
  - Likely effective, but only 1 open label study, many case series or retrospective studies, but no RCTs (yet!)
- Depression
  - Mostly case series and retrospective reviews, but almost all treated had favorable responses
  - From studies (including RCT) of elderly without dementia, remission consistently faster and at a higher rate than with medications
  - Older patients are MORE likely to respond to ECT
- ECT may improve motor symptoms in PD

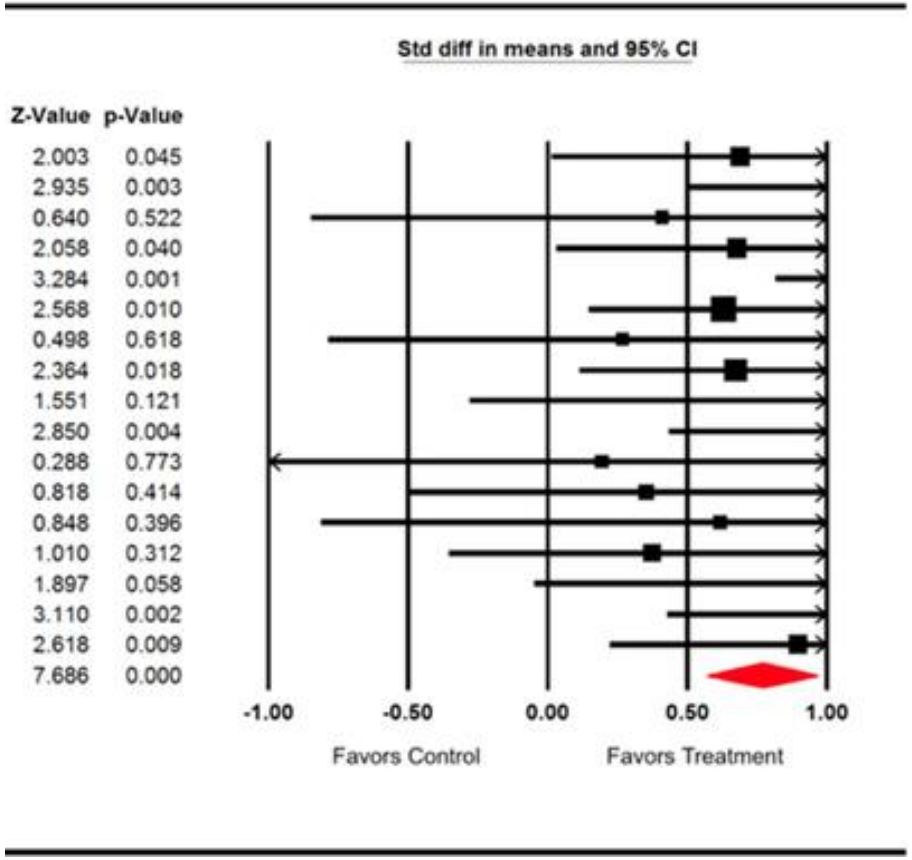


Meyer 2018, Kaster 2021, Stella 2023, Bachu 2023

Transcranial Magnetic Stimulation in Dementia

- FDA approved for MDD and OCD independent of dementia
- Transdiagnostic very small improvement in working memory for TMS in meta-analysis but no decline
- Meta-analysis of 13 small studies suggest TMS benefits cognition in AD
- 11 studies for TMS and psychiatric symptoms
  - 2 out of 3 showing improvement for apathy
  - 6 out of 7 showing benefit for overall symptoms
  - Some sub-analysis suggested improvements in aggression/agitation, though unclear if clinically meaningful changes
  - Often secondary analyses
- Issues with consent and feasibility for those with worse cognition or more agitation

TMS for Cognition in AD



Begemann 2020, Chou 2020, Murphy 2023

Case 5

83yo F h/o hypothyroidism, chronic DVT on aspirin, essential thrombocytosis on hydroxyurea, aortic stenosis, and remote TBI presents with decreased motivation. Husband notes that the patient is much less motivated and the "whole world has collapsed that she used to do." Pt notes that "I just don't have the interest in them (hobbies)." Reduced socialization, and patient notes it's because "nobody listens to me." Husband notes that he has been trying to get her to be more engaged socially, but he notes that if he doesn't push her, she doesn't want to "do the things she used to do." She denies poor mood, and her husband has not noted tearfulness or clear dysphoria. She has a family history of late-onset dementias, has progressive difficulty remembering names of familiar people, makes progressive mistakes when trying to complete complex tasks like cooking, and has a MOCA of 18/30. While her cognitive issues have been going on for years, she has started to show stooped posture, acting out dreams, reduced gait speed with minimal arm swing, hypophonia, masked facies, and visual hallucinations.

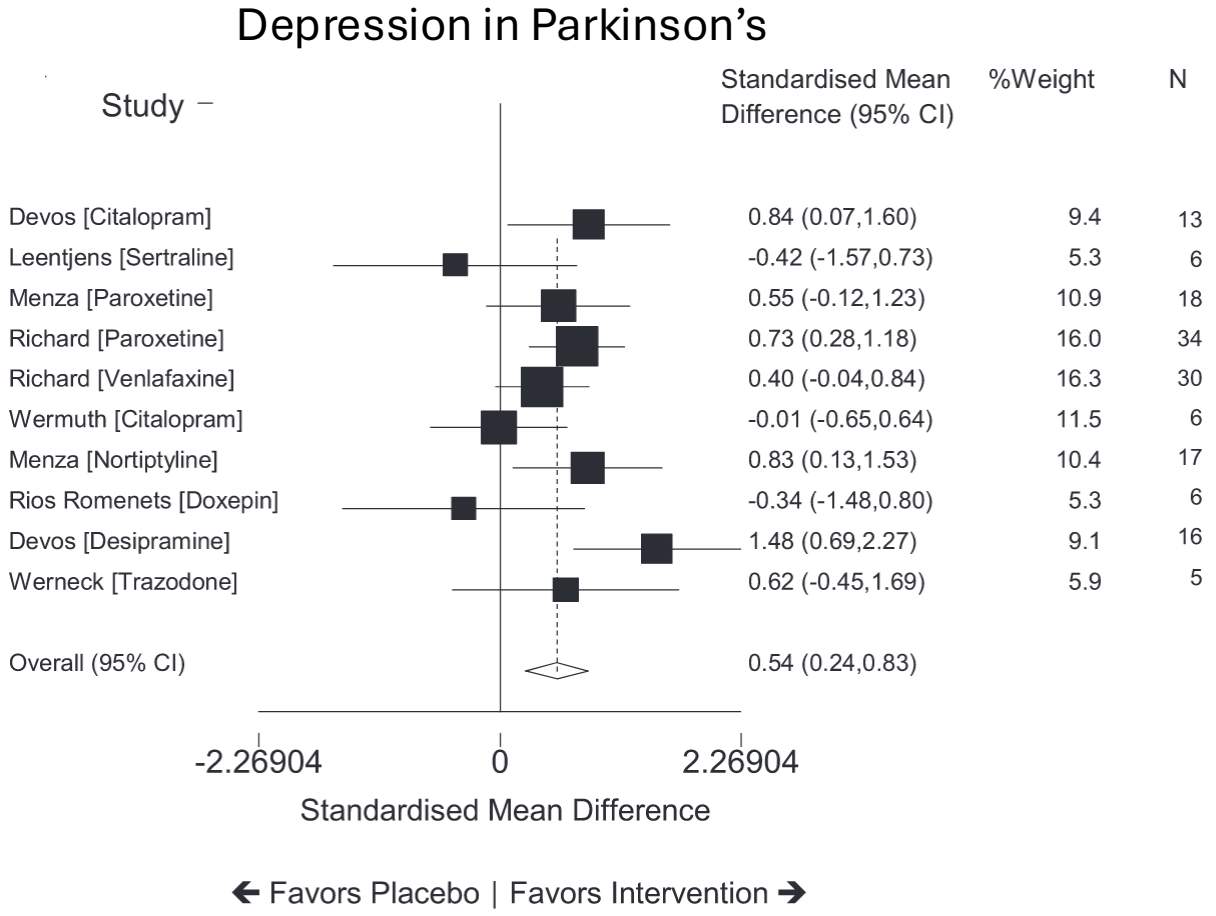
Depression and Apathy

- The most common psychiatric symptoms in dementia are affective (depression, apathy, anxiety)
- Apathy is defined as decrease in 2 of 3 areas
  - Interest
  - Initiative
  - Emotional Expression
- With dementia affecting multiple domains, apathy + dementia can easily fulfill MDD criteria
  - Sleep Changes
  - “Anhedonia”
  - Fatigue, decreased energy
  - Decreases in cognition/concentration
  - Changes in appetite
  - Psychomotor changes
- Bottom line: Antidepressants don’t fix apathy, so if you diagnose depression, confirm dysphoria

Fisher 2023, Miller 2021, Lanctot 2023

Depression Pharmacology in Dementia

- Canonically, depression in Alzheimer's is refractory to antidepressants
  - HTA-SADD trial: no improvement with sertraline and mirtazapine
  - Cochrane meta-analysis: no benefit of SSRI as class
- Conversely, a number of serotonergic antidepressants are effective in Parkinson's Disease, though LBD and PDD are less well studied
- However, depression is almost always identified by MDD diagnosis -> diagnostic ambiguity with apathy?



Banerjee 2011, Dudas 2018, Bomasang-Layno 2015

Apathy Pharmacology in Dementia

- ADMET-1 and ADMET-2: moderate evidence for improvement of apathy in AD with methylphenidate without changes in weight
- Mixed and poorly controlled studies for cholinesterase inhibitors and apathy; studies for memantine are also sparse and mixed
  - Rivastigmine has some good RCT evidence for improvement of apathy in PD
- One RCT for modafinil showed no improvement
- Antidepressants, including bupropion, have not generally shown improvements in apathy
- Agomelatonin over melatonin was shown to improve apathy in one RCT for FTD
- Intranasal oxytocin for FTD (FOXY) trial for apathy led to signicicant improvement at 6 weeks

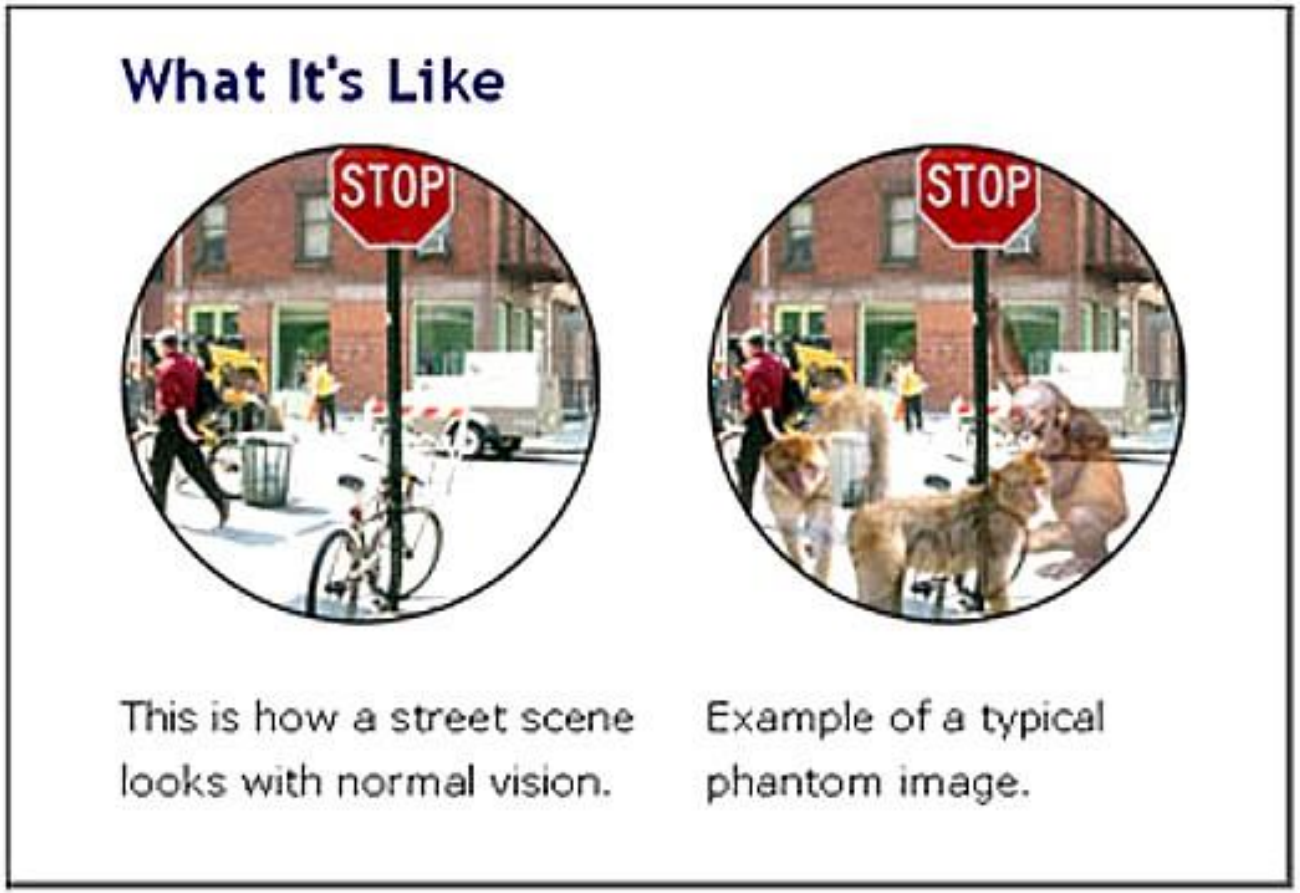
Mintzer 2021, Harrison 2016, Theleritis 2023

Case 6

88 year old male with history of bullous pemphigoid s/p prednisone, glaucoma and blindness presents with “continual presence of hallucinations”. Patient noted visual hallucinations started around many months prior after IV steroid treatment for bullous pemphigoid and a prolonged hospital stay. While in hospital, he often would experience see people, such as "two young girls from the middle east with conical hats... when I'd wake up, they'd be sitting on my beds." Though visual hallucinations persisted after hospitalization, they changed in quality with time, and he endorses sometimes feeling like he's in an auditorium with many people or seeing the world as static and moving through it. Though not directly distressing, he notes the hallucinations are ”not reality… they sort of interfere with short term planning", such as once when he saw a dropoff at the threshold of his bathroom and was afraid to move forward. The patient was unclear how the hallucinations changed with timing of visual loss due to glaucoma. The patient also notes cognitive deficits including repeating questions and disorientation with worsening of cognition in the afternoon. Mostly independent in ADLs but struggles with some iADLs due to blindness and cognitive issues. No clear motor changes; acts out dreams but stopped when given melatonin, and he denies other sleep issues. Initial MOCA 13/22 (limited by vision and hearing loss). MRI with moderate atrophy in typical AD pattern and a few microhemorrhages. Elevated PSA a year ago, but he does not want to move forward with biopsy or treatment.

Charles Bonnet Syndrome

- Hallucinations in the setting of sensory impairments
  - Often musical-like for auditory
  - Visual hallucinations can be simple or complex
  - Any etiology that can reduce sensory input can cause these hallucinations
  - Onset follows progression: Acute progression, acute onset; slow progression/slow onset
- Treatment
  - 60% are unbothered by hallucinations
  - Optimizing sensory function may reduce or stop hallucinations
  - For those with cognitive impairment, acetylcholine esterase inhibitors can help
  - Anecdotal evidence for others: valproate, carbamazepine, gabapentin, clonazepam, venlafaxine, and escitalopram



Rojas 2023

Main Takeaways

- Behavioral interventions are FIRST LINE
- SSRIs are your friend, unless you suspect apathy. Lexapro/Citalopram and sertraline are particularly nice in older adults (fewer drug-drug interactions)
- Antipsychotics help a little for agitation, but keep them low and routinely reassess if they're needed
- Don't forget about ECT in difficult to treat cases