

Psychopharmacology: Neuropsychiatric Syndromes

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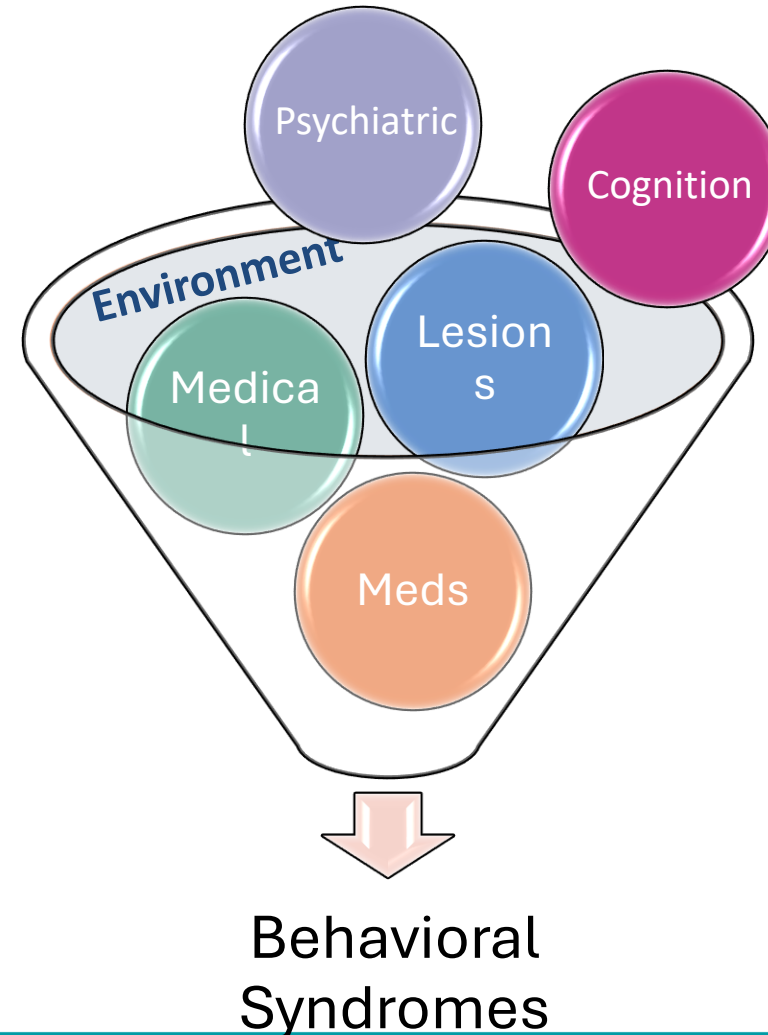
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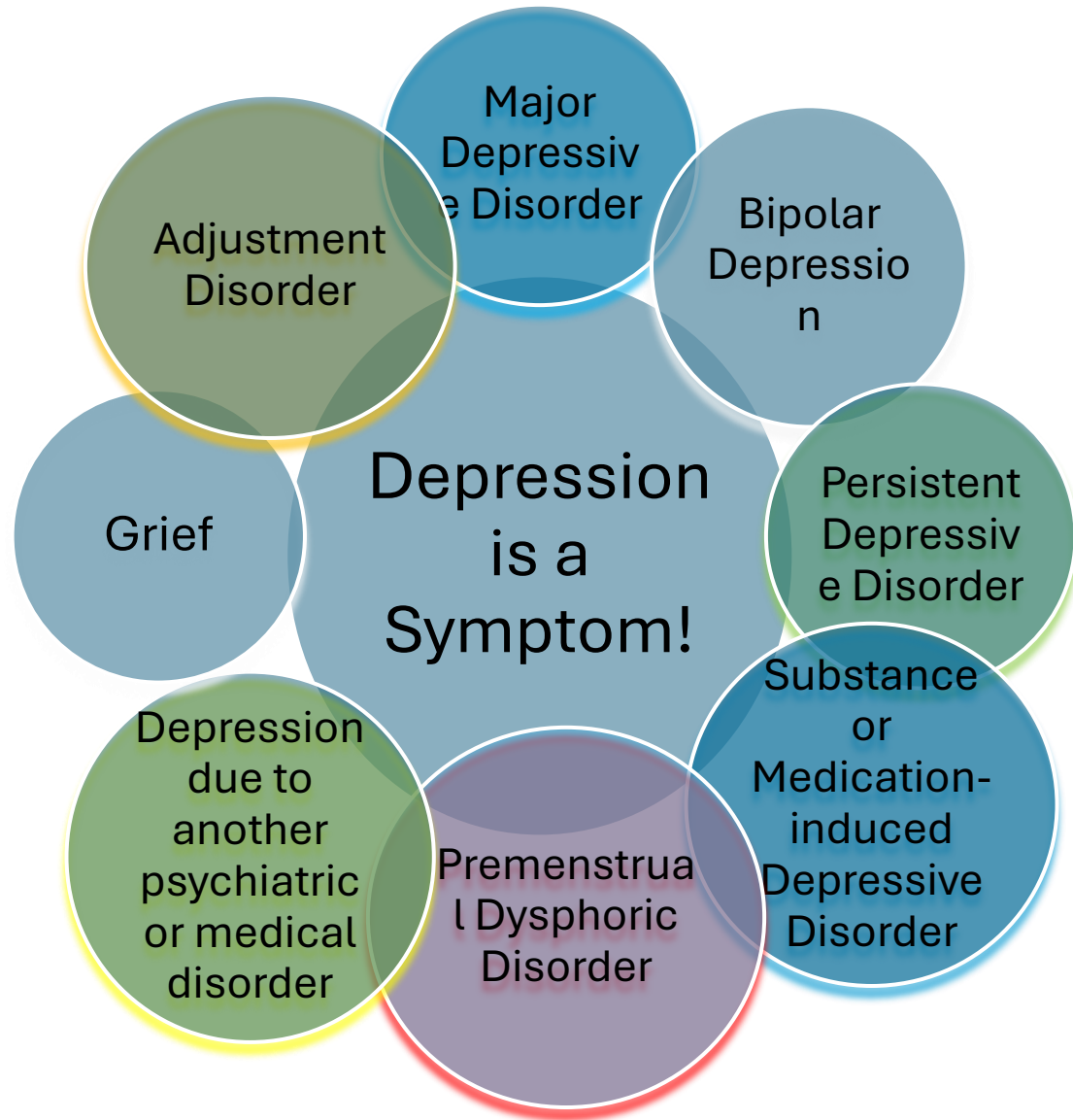
Multifactorial Etiology of Neuropsychiatric Syndromes

- Localizable lesions
- Neurocircuitry abnormalities
- Neurotransmitter and neuromodulator changes
- Cognitive dysfunction
- Medical comorbidity
- Concomitant medications
- Primarily psychiatric
- Psychosocial and environmental factors



Pharmacotherapy of Selected Neuropsychiatric Syndromes

- Depression
 - Refresher on general guidelines
 - General tips on managing depression in neurologic disorders
 - Vascular depression
 - Post-stroke
- Anxiety
- Irritability
- Apathy
- Psychosis



The diagnosis *and treatment* of depression depends on its etiology, severity, associated disorders, and cultural context

MAJOR DEPRESSIVE DISORDER: DSM-5 DIAGNOSTIC CRITERIA

Box 1 | Definition of MDD according to DSM-5

- An individual will show five (or more) of the following symptoms, which should be present during the same 2-week period nearly every day and should represent a change from previous functioning:
 - Depressed mood*
 - Markedly diminished interest or pleasure in all, or almost all, activities*
 - Considerable weight loss when not dieting, weight gain, or decrease or increase in appetite
 - Insomnia or hypersomnia
 - Psychomotor agitation or retardation
 - Fatigue or loss of energy
 - Feelings of worthlessness, or excessive or inappropriate guilt, which might be delusional; that is, not merely self-reproach or guilt about being sick
 - Diminished ability to think or concentrate, or indecisiveness
 - Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan; the individual has made a suicide attempt or a specific plan for committing suicide

*Depressed mood and/or diminished interest or pleasure must be evident for a diagnosis.

Sleep, disturbances

Interest, diminished

Guilt, excessive

Energy, diminished

Concentration, reduced

Appetite, changes

P psychomotor retardation/
agitation

Suicide, thoughts or attempts

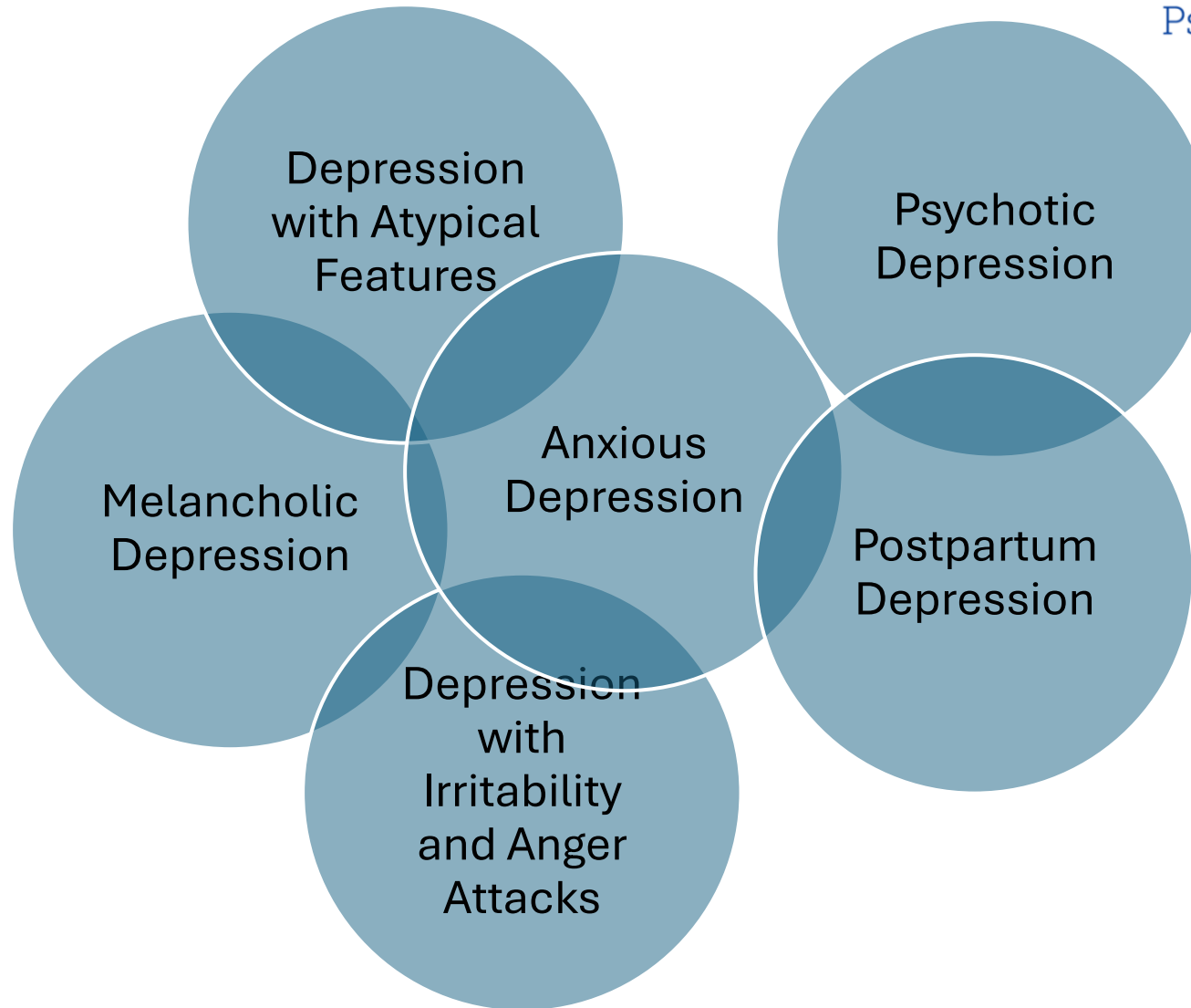
Otte et al, Nat Rev Dis

Primers. 2016 Sep

15;2:16065. doi:

10.1038/nrdp.2016.65.

Heterogeneity of Major Depressive Disorder



Screening for Clinically Significant Depression: The Patient Health Questionnaire (PHQ)-2

Over the past 2 weeks, how often have you been bothered by any of the following problems?	Not At all	Several Days	More Than Half the Days	Nearly Every Day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed or hopeless	0	1	2	3

Score of ≥ 3 : 83% sensitivity, 92% specificity
(Score of ≥ 1 : 96% sensitivity, 57% specificity)

Levis B et al, *JAMA*. 2020 Jun 9;323(22):2290-2300

PHQ-9 score indicates severity, guides treatment planning, and gauges treatment response

PHQ-9 Score	Severity of Depression	Proposed Treatment Plan <i>ONCE Patient Fully Assessed</i>	
0-4	None	None	
5-9	Mild	Watchful waiting, optimize self-care, improve nutrition and physical activity; repeat PHQ-9 at follow up	
10-14	Moderate	Medication and/or psychotherapy and/or digital apps	
15-19	Moderately Severe	Medication and encourage depression-focused psychotherapy	
20-27	Severe	Medication and supportive therapy	
Spitzer RL (JAMA 1999); Kroenke K (J Gen Intern Med 2001)			

Treatment Options for MDD

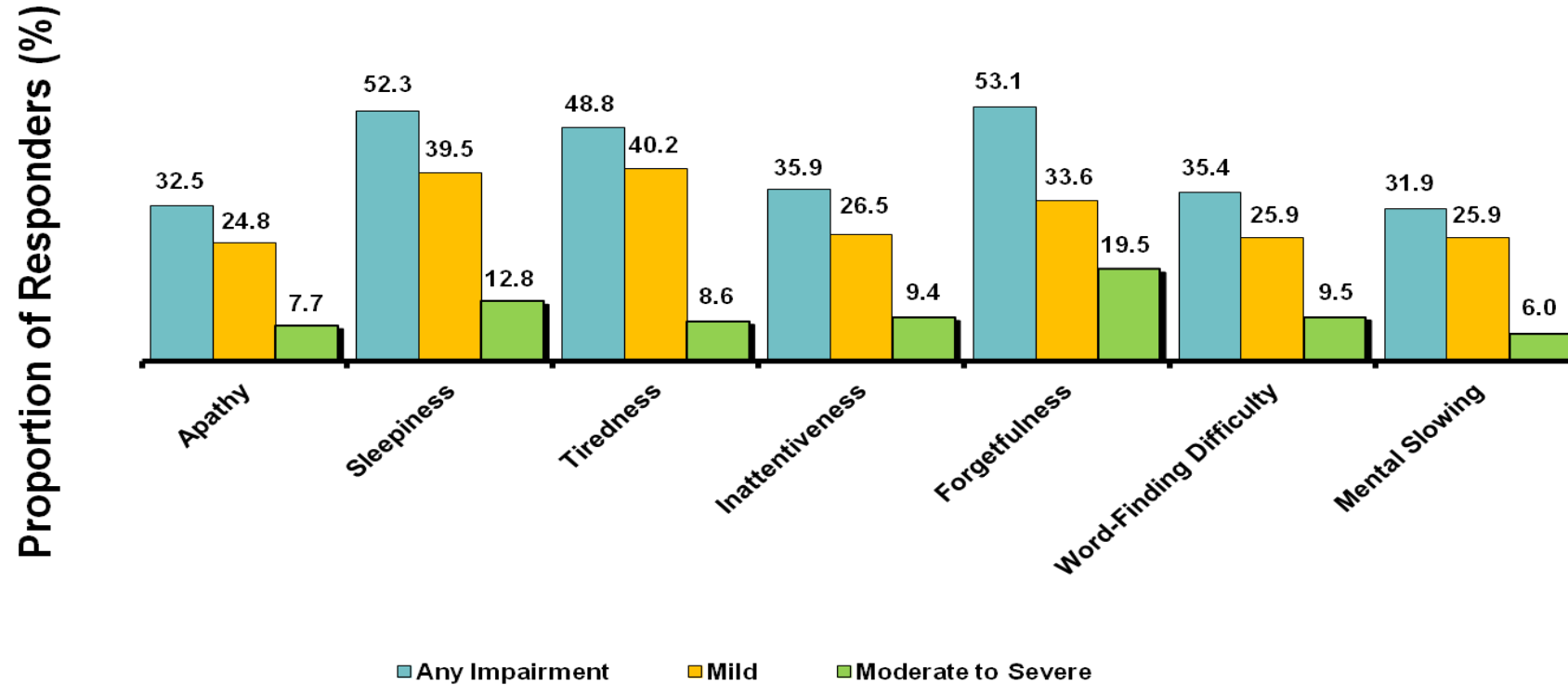
- **Psychosocial Therapies** (e.g., *CBT, IPT*)
 - None of these therapies are easy to perform well and access is limited
- **Pharmacological Therapies** (all are monoamine-based)
 - *Selective Serotonin Reuptake Inhibitors (SSRIs)*
 - Most common first-line treatment
 - *Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)*
 - May be superior to SSRIs in some populations
 - *Atypical Antidepressants*
 - Mirtazapine (Remeron), Bupropion (Wellbutrin), Vortioxetine (Brintellix)
 - *Tricyclic Antidepressants (TCAs)*
 - Generic TCAs are very inexpensive but have significant risk for AEs
 - *MAOI Inhibitors*
 - Very rarely prescribed because of risks of AEs or drug-drug interactions
- **Somatic Therapies**
 - Electroconvulsive treatment (ECT) and Vagal nerve stimulation (VNS) – only for refractory forms
 - Rapid transcranial magnetic stimulation (rTMS) - Frequency of administration quite burdensome
- **Alternative and Natural Therapies**
 - SAMe, St.John's Wort, Omega-3 Fatty Acids and others less well studied
- **Digital Therapies**
 - Rejoyn (CT-152): FDA-approved app as augmentation for MDD patients on antidepressants

Evidence-Based Pharmacotherapy of Non-bipolar, Non-Psychotic Depression—General Guidelines

- Second-generation antidepressant
 - Past positive response or FH of good response to Rx? → Rx it!
 - No active eating disorder or other seizure risk, or panic attacks → consider bupropion
 - Particularly severe or treatment-refractory depression or anxiety sx? → SNRI or MAOI
 - Insomnia and/or poor appetite? → mirtazapine
 - On multiple medications → venlafaxine or mirtazapine
 - Prominent irritability → SSRI
- Always consider drug-drug interactions and side-effects, setting expectations on the latter and also selecting according to side-effect profile
- Rx enough for long enough, potentially 8-12 weeks to assess response, and then once remitted, continuation therapy for all and maintenance therapy for chronic and recurrent illness
- Always inquire about adherence and tolerability

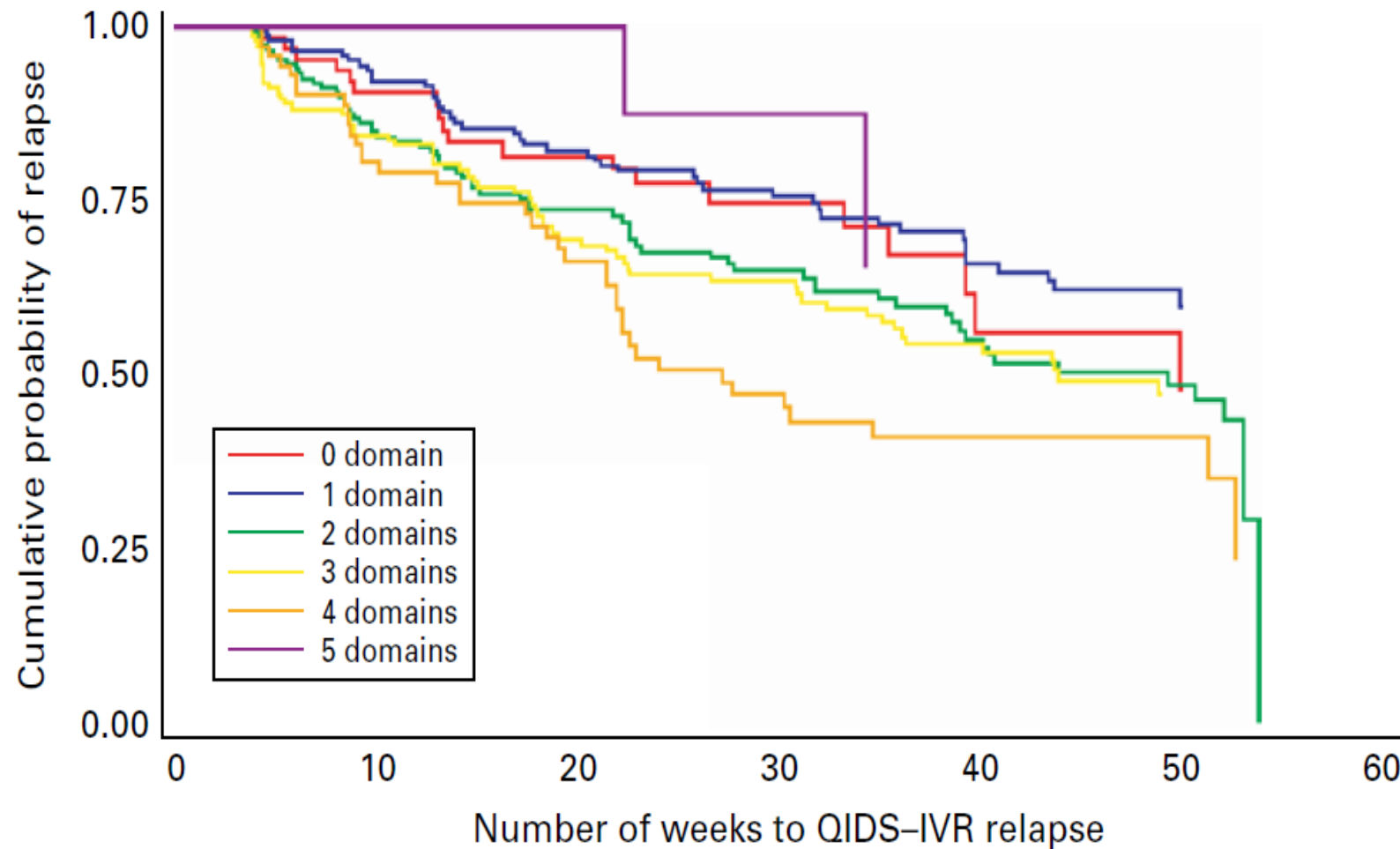
MacQueen G, Santaguida P, Keshavarz H, Jaworska N, Levine M, Beyene J, Raina P. Systematic Review of Clinical Practice Guidelines for Failed Antidepressant Treatment Response in Major Depressive Disorder, Dysthymia, and Subthreshold Depression in Adults. *Can J Psychiatry*. 2017 Jan;62(1):11-23

Proportion of MDD Subjects with Residual Physical and Cognitive Deficits (N=117) Following Antidepressant Treatment



Fava M et al, J Clin Psych 2006; 67: 1754-1759

Residual Symptoms Predict Relapse in Remitters to Citalopram in STAR*D Level 1



Nierenberg AA, Husain MM, Trivedi MH, Fava M, Warden D, Wisniewski SR, Miyahara S, Rush AJ. Psychol Med. 2009;22:1-10.

Next Steps When Plan A Fails...

- Always screen for other impediments , eg complicated psychosocial situation, incomplete adherence, or undisclosed substance use or eating disorder. If no signals of response, switch to another antidepressant
- Combine with another antidepressant if responding but not fully remitting:
 - Bupropion or Bupropion plus dextromethorphan
 - Mirtazapine
- Augment if responding but not fully remitting
 - Buspirone- titrate to at least 20-30mg daily
 - T3 – 50 mcg daily
 - Second generation antipsychotic (all FDA-approved)
 - Aripiprazole- watch for insomnia, akathisia, fasting glucose/A1c
 - Quetiapine- watch for dizziness, metabolic issues, sedation
 - Lumateperone- watch for metabolic issues, sedation, dizziness
 - Cariprazine- watch for akathisia, sedation
 - Brexpiprazole- watch for akathisia, insomnia, fasting glucose/A1c
 - Dopaminergic drugs and psychostimulants
 - Glutamatergic drugs (e.g., ketamine, esketamine) or GABAergic drugs (e.g., zuranolone)
 - Psychedelics

Double-blind, Placebo-controlled, Dose-ranging Trial of Intravenous Ketamine as Adjunctive Therapy in Treatment-Resistant Depression (TRD)

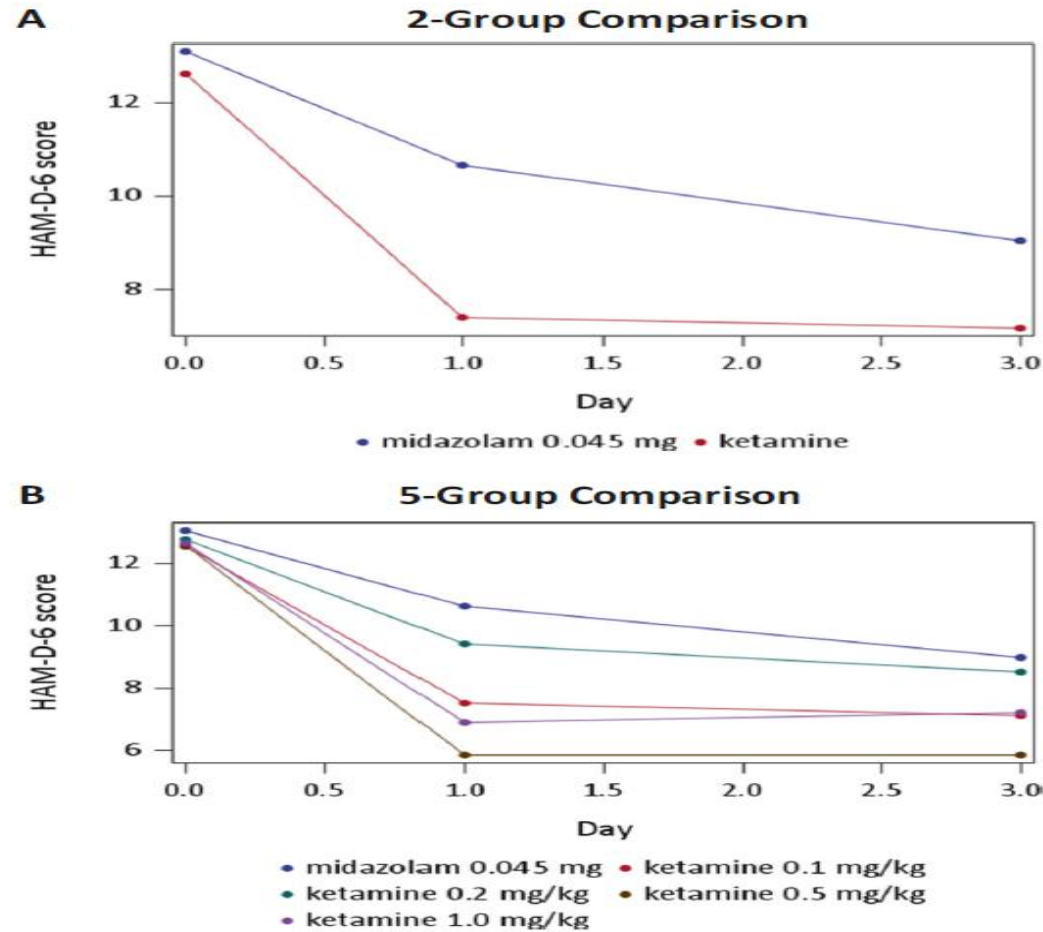
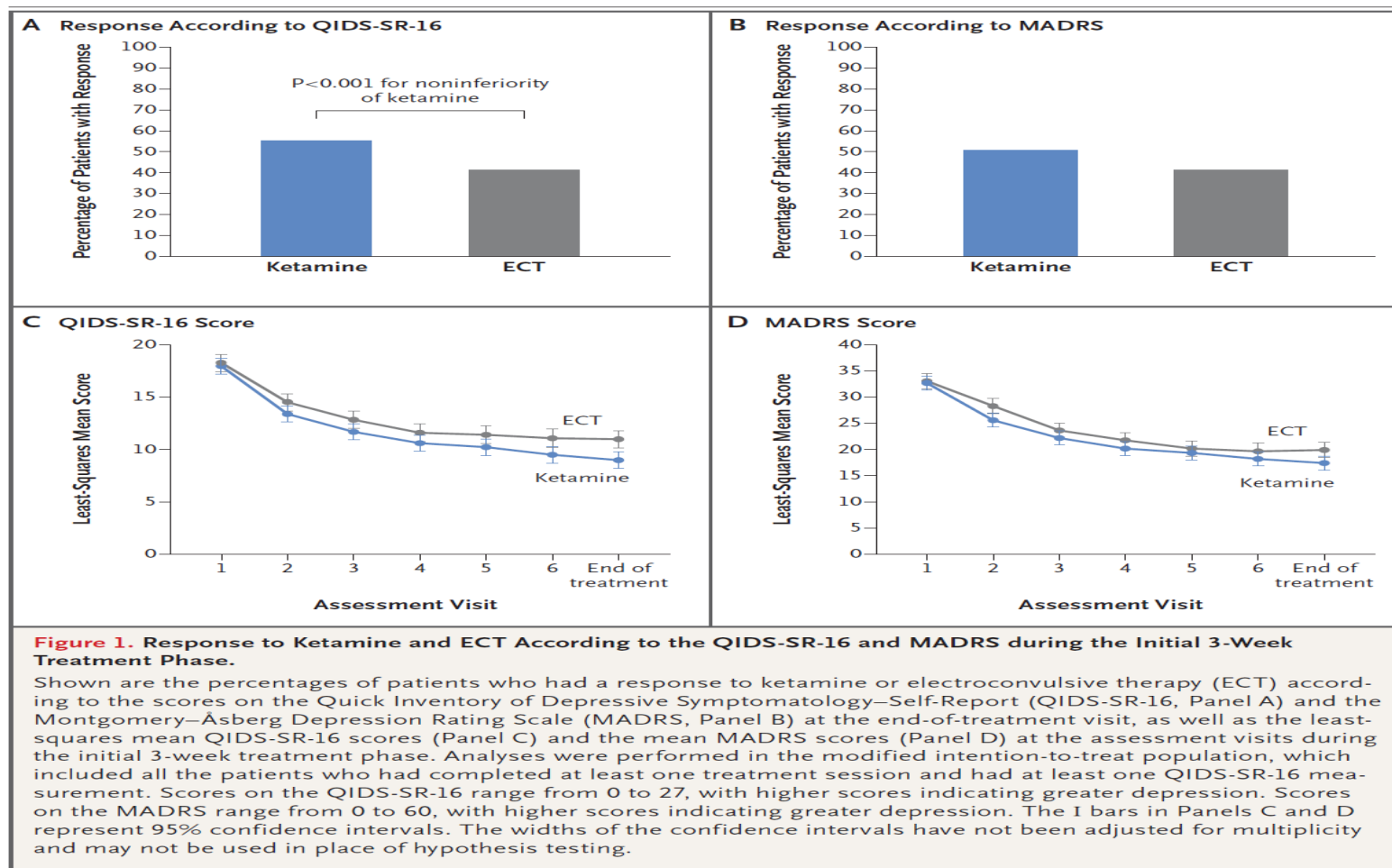


Fig. 2 HAM-D-6 scores over the first 72 h of treatment; Fig. 2A reports the 2-group analysis; Fig. 2B reports the 5-group analysis;

Fava et al
Molecular Psychiatry
<https://doi.org/10.1038/s41380-018-0256-5>

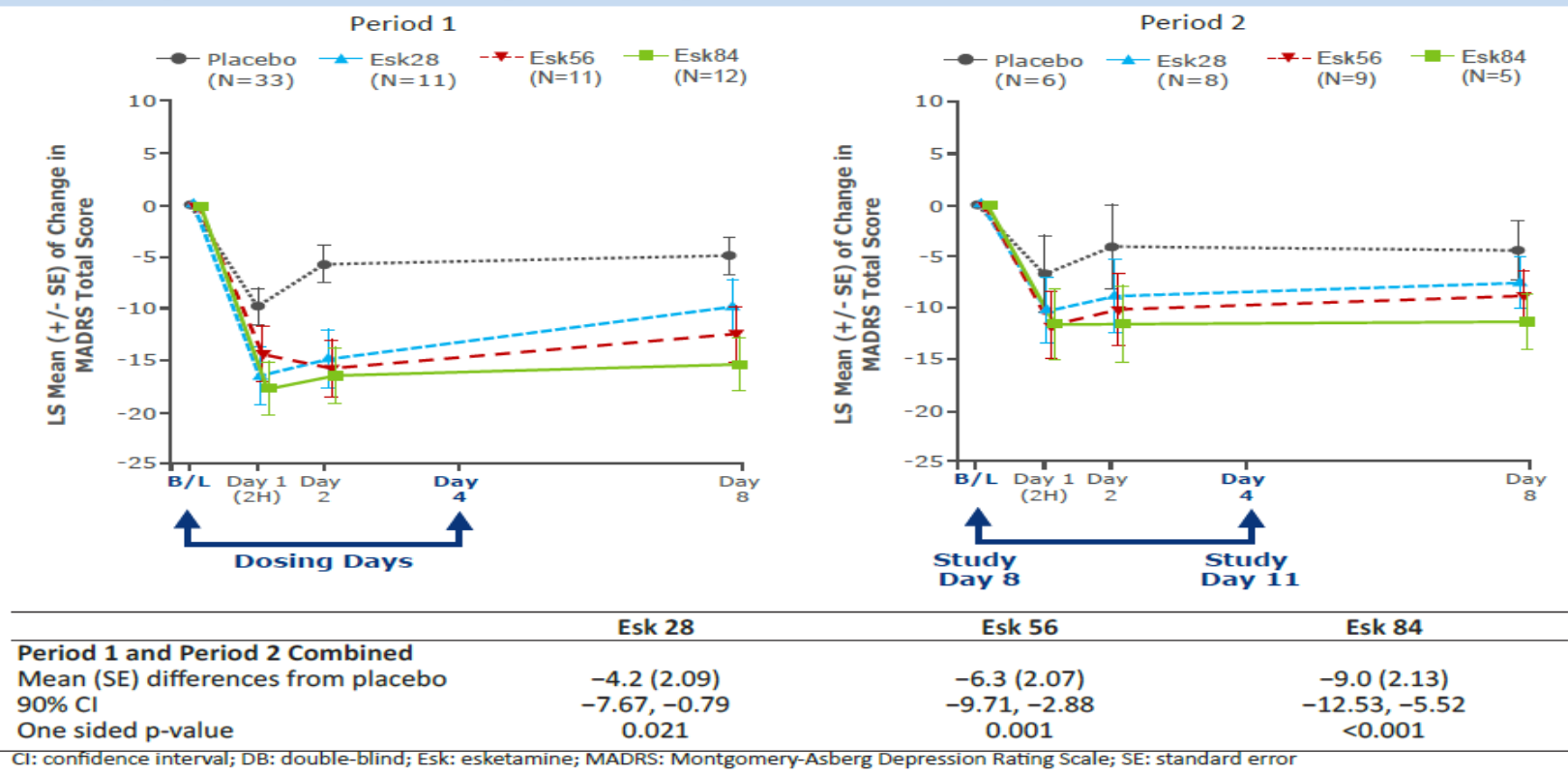
Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression (n=403)



Anand, et al. *N Engl J Med* 2023;388:2315-25.

A Double-Blind, Doubly-Randomized, Placebo-Controlled Study of Intranasal Esketamine in TRD*

Figure 2: MADRS Total Score LS Mean Change from Baseline to End Point – ANCOVA LOCF Analysis (Intent-to-Treat Analysis Set-DB)

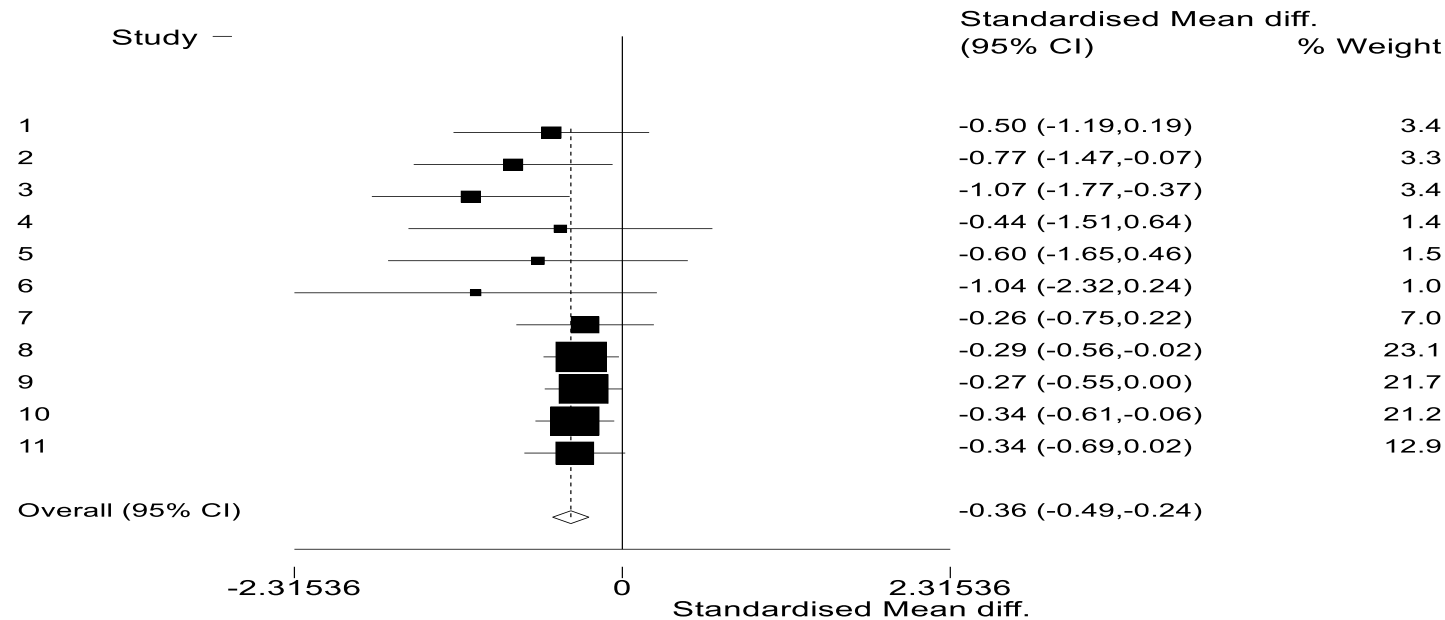


- Assuming equal variance across treatments and periods, the effect size combining both periods ranged from 0.52 for 28 mg, 0.92 for 56 mg, and 1.20 for 84 mg esketamine

*TRD assessed with the ATRQ; Singh et al, Biol Psychiatry. 2016 Sep 15;80(6):424-31.

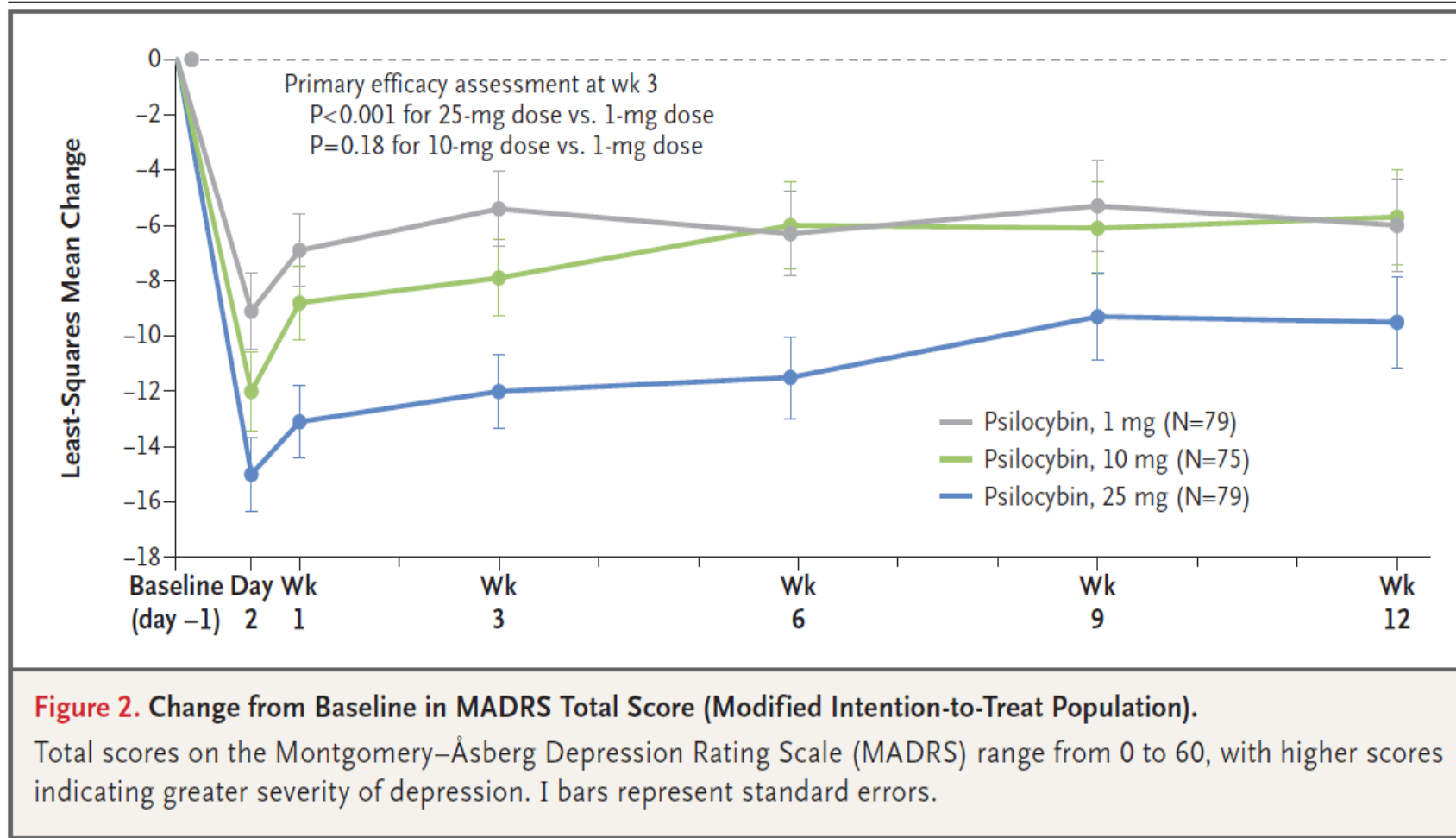
Meta-Analysis of Esketamine Augmentation in TRD Studies

Figure 1: Forest Plot of SMD in change in primary outcome scores between adjunctive esketamine and placebo



Papakostas et al, J Clin Psychiatry. 2020 May 26;81(4):19r12889. doi: 10.4088/JCP.19r12889.

Psilocybin in Treatment Resistant Depression (TRD)



Goodwin et al, N Engl J Med 2022;387:1637-48. DOI: 10.1056/NEJMoa2206443

Depression Treatment Considerations in Neuropsychiatric Patients

- Many antidepressants may disrupt sleep → aim for lowest dose with maximal benefits
- SSRIs can aggravate apathy → low dose stimulant or modafinil can be added
- Anticholinergic effects of TCAs and paroxetine can aggravate confusion/ cognitive deficits
- Differentiate depression from pseudobulbar affect (PBA), present in many neurologic disorders (eg CVA, TBI, AD, MS, PD, ALS)
- Bupropion IR and doses above 450 mg/day are especially apt to lower seizure threshold
- Important to review status of underlying neurological condition (e.g., depression as signal of MS relapse, or prodromal symptoms of AD and PD; etc)
- Vortioxetine preliminary data for depression in older adults with cognitive impairment is promising for its pro-cognitive effects
 - 3 RCTs though populations, vortioxetine dosing, and primary endpoints and measurement tools very different

Wichniak, A., Wierzbicka, A., Wałęcka, M. *et al.* *Effects of Antidepressants on Sleep.* *Curr Psychiatry Rep* **19**, 63 (2017)

Nice review: Bishop MM, Fixen DR, Linnebur SA, Pearson SM. *Cognitive effects of vortioxetine in older adults: a systematic review.* *Ther Adv Psychopharmacol.* 2021 Jul 22;11:1-10

Vascular Depression

- A subtype of later-life-onset depression (>60)
- Core features include:
 - Executive dysfunction—psychomotor slowing, reduced motivation, poor initiative, impaired processing speed and concentration—and low energy
 - Anhedonia > depressed mood
 - Absence of FH of depression
 - Cerebrovascular risk factors—eg HTN, DM, dyslipidemia
 - Multiple deep white matter hyper-intensities on MRI which disrupt frontal-subcortical pathways
 - Poor treatment response
- Persistently high or increasing levels of late life depression correlate highly with future risk of dementia
- Treatment may best be focused on prevention of CV risk factors and minimizing Rxs which might aggravate symptoms

Aizenstein et al, *BMC Medicine*, 2016; 14:161; Tubi MA, Feingold FW, Kothapalli D, Hare ET, King KS, Thompson PM, Braskie MN; Alzheimer's Disease Neuroimaging Initiative. White matter hyperintensities and their relationship to cognition: Effects of segmentation algorithm. *Neuroimage*. 2020 Feb 1;206:116327

Post-Stroke Depression

- ~1/3 of ischemic stroke survivors and the most common psychiatric complication
- Associated with increased mortality, physical/social disability, and increased cognitive issues → poor QOL
- It is not just a reaction to an abrupt loss and capacity to function
 - Lesion location *especially* predictive of depression emerging shortly after stroke
 - Stroke-induced HPA axis hyperactivity
 - Pro-inflammatory cytokines
 - Reduced BDNF → alterations in neuroplasticity and neurogenesis
 - Increased intestinal permeability
- Differentiate from PBA, apathy, fatigue, and anosognosia
- Evidence guiding treatment is limited though supports efficacy of antidepressants
- Preclinical evidence suggests that MAOIs have neuroprotective effects post-stroke
- Emerging evidence supports TMS as helpful
- Very preliminary: ashwaganda, acupuncture, acupressure, neuroprotective diets might hold promise

Guo J, Wang J, Sun W, Liu X. *J Neurol*. 2022 Mar;269(3):1236-1249; Zhou L, Wang T, Yu Y, Li M, Sun X, Song W, Wang Y, Zhang C, Fu F. *Biomed Pharmacother*. 2022 Jul;151:113146; Kato et al, *Biol Pharm Bull*. 2000 Apr;23(4):406-10. doi: 10.1248/bpb.23.406; Narushima, Kosier, Robinson, *J Neuropsychiatry*, 2003;15(4):422-430; Mayberg, Robinson, Wong, *Am J Psychiatry*, 1988;145:937-943; Whyte, Mulsant, *Biol Psychiatry*, 2002;52(3):253-264; Robinson and Jorge, *Am J Psychiatry*, 2016;173(3):221-231;

Anxiety is Common in Neurologic Disorders

- Anxiety can be either a reaction or a symptom or a disorder
- Most primary anxiety disorders start early in life, though generalized anxiety disorder and phobias (falling and agoraphobia) have a second peak in late life
 - Nonetheless, emergence of anxiety later in life can be an early signal of an evolving neurologic process, e.g. dementia
- Anxiety can be the vehicle for expressing something else, e.g. pain
- Very commonly co-occurs with depression
- Untreated anxiety aggravates cognitive symptoms and leads to worse outcomes
- Diseased neural substrate increases risk of paradoxical reactions, i.e. increased anxiety in response to benzodiazepines and antihistamines
- Generally best to avoid benzodiazepines and any agent with anticholinergic effects in treating anxiety given adverse cognitive effects
- Gabapentin or pregabalin can be used effectively
- Atypical antipsychotics can help but may be too sedating and cause EPS
- Optimize non-pharmacologic interventions!

Schuurmans J, van Balkom A. *Curr Psychiatry Rep.* 2011 Aug;13(4):267-73

Anxiety Pharmacotherapy in the Elderly or Neurologically Impaired: Antidepressants

	Consider	Caution	Side-effects
SSRIs	- Sertraline - Escitalopram - Citalopram	- Paroxetine (confusion, 2D6 inhibitor) - Fluoxetine (2D6 inhibitor) - Citalopram and escitalopram QTc prolongation: <i>patients taking additional pro-arrhythmic drugs, that have underlying genetic disposition for acquired long-QT syndrome, that are >65 years, or have conditions predisposing them for triggering arrhythmias, should be monitored with therapeutic drug monitoring (TDM). Serum concentrations of escitalopram (Cmin) should be kept below 100 nM, to avoid pro-arrhythmic effect!</i> (Faraj et al, <i>The Lancet</i>, Vol 95; 104779, SEPTEMBER 2023)	- Nausea, sedation, insomnia, sexual dysfunction - Increased risk of bleeding (GI, CNS) - Weight gain - SIADH
SNRIs	Venlafaxine (no P450 inhibition) or desvenlafaxine	Duloxetine (moderate 2D6 inhibitor, rare hepatic toxicity)	- Increased BP especially with venlafaxine - Side effect profile similar to SSRIs
TCAs and MAOIs		Generally avoid due to anti-cholinergic burden, risk of falls	
Mirtazapine	Promotes sleep and appetite, lacks meaningful P450 inhibition		- Sedation - Weight gain - Increased risk for bleeding (Na et al, <i>J Affect Disord</i>. 2018 Jan 1;225:221-226.
Vortioxetine	- Emerging evidence of pro-cognitive benefits - Potent SRI increases NE and DA in medial PFC		- More nausea than other SRIs - SRI activity → likely to have bleeding risks although no evidence yet

Anxiety Pharmacotherapy in the Elderly or Neurologically Impaired: Non-Antidepressant Class Medications

	Consider	Caution	Side-effects
Buspirone	• 5HT1a partial agonist • No RCTs in elderly though in theory should be well-tolerated • Case reports of benefits in dementia for anxiety/agitation when used as prn	• Takes weeks to months for full benefits (prn benefit poorly understood)	• Low risk for falls, adverse cognitive effects, or respiratory depression • Nausea, headaches, mild sedation can occur
Benzodiazepines	• Due to risks, minimize use • Lorazepam preferred due to no active metabolites and non-oxidative metabolism	• Very high risk for falls, fractures, cognitive impairment • Educate re avoiding prior to driving	
Atypical antipsychotics	• Quetiapine (+evidence GAD) • Cariprazine (Fava et al, J Clin Psychiatry. 2025 Apr online) • Low-dose risperidone or olanzapine • Brexpiprazole now FDA-approved for agitation in dementia though there are serious safety concerns (Whitaker, <i>BMJ</i> 2023;382:p1801)	• Black box warning re: increased mortality in dementia	• Metabolic risks especially olanzapine and higher dose quetiapine • EPS/TD with risperidone, less with olanzapine and quetiapine • Hyperprolactinemia with risperidone

Adapted from Crocco et al, Curr Treat Options Psychiatry 2017 March; 4(1)

Anxiety Pharmacotherapy in the Elderly or Neurologically Impaired: Noradrenergic Agents and Gabapentinoids

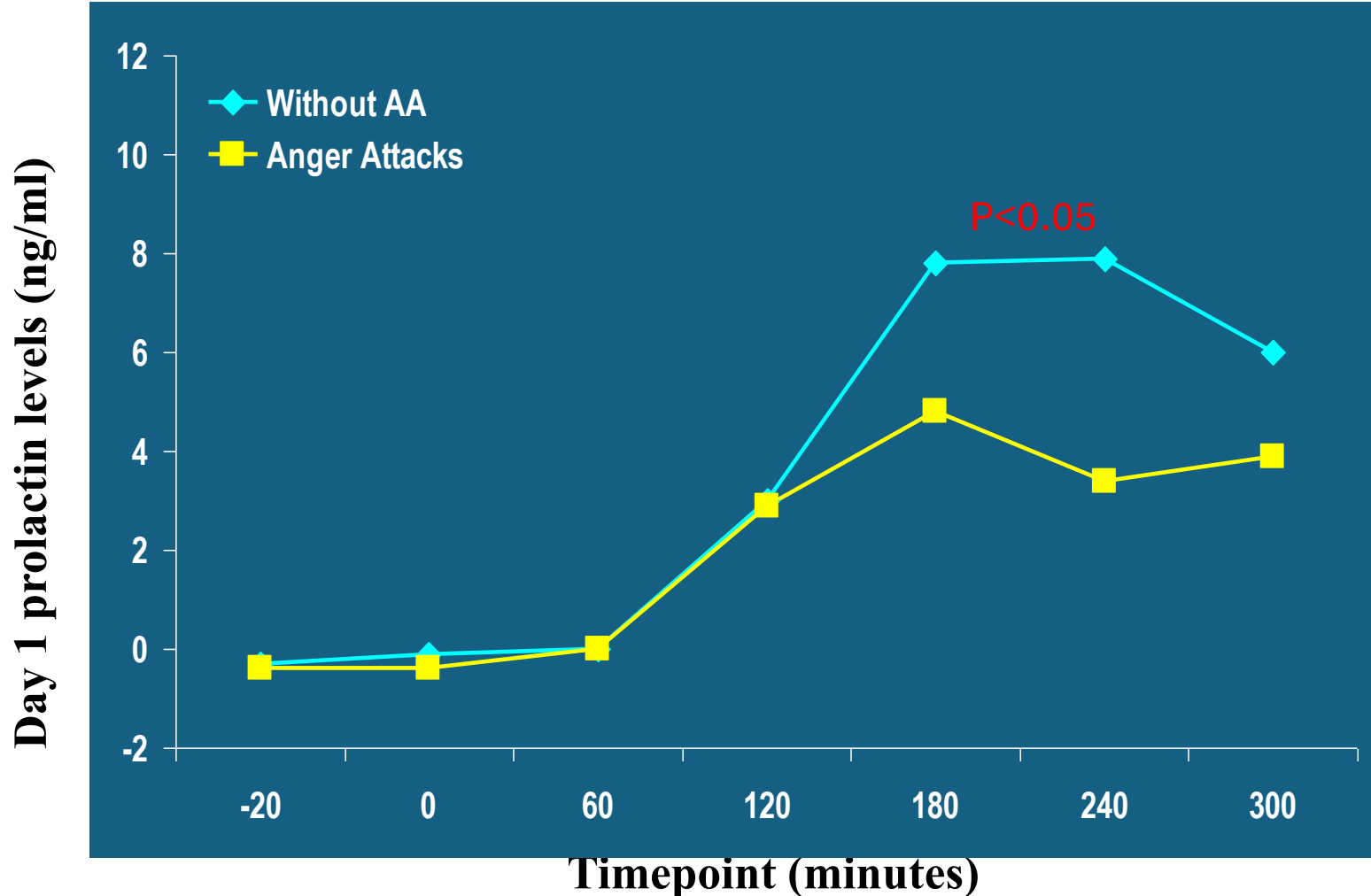
Consider		Caution	Side-effects
Beta blockers	Only evidence is for treatment of performance-type anxiety in non-elderly adults	Case studies of metoprolol inducing anxiety in elderly	- Can be mild depressant - Sedation for some agents - Disrupt sleep
Prazosin	RCT + for agitation in dementia (Wang; RCT n=22, started 1mg qd titrated up to 6mg qd x 8 wks)	Low risk of respiratory depression when combined with other CNS depressants or in those with pre-existing respiratory conditions.	dizziness, headaches, drowsiness, fatigue, weakness, palpitations, hypotension and nausea
Gabapentin and pregabalin	Across the anxiety spectrum, a consistent but not universal effect in favor of gabapentinoids compared to placebo was seen in systematic review (Hong et al, Mol Psychiatry 2022 Mar;27(3):1339-1349.)	Fall risk though in dementia study very well tolerated	drowsiness, dizziness, blurred vision, and gastrointestinal issues

Wang LY et al. Am J Geriatr Psychiatry. 2009 Sep;17(9):744-51; Brismar K et al, Acta Med Scand. 1988;223(6):525-30

Irritability is Common in Neurologic Disorders

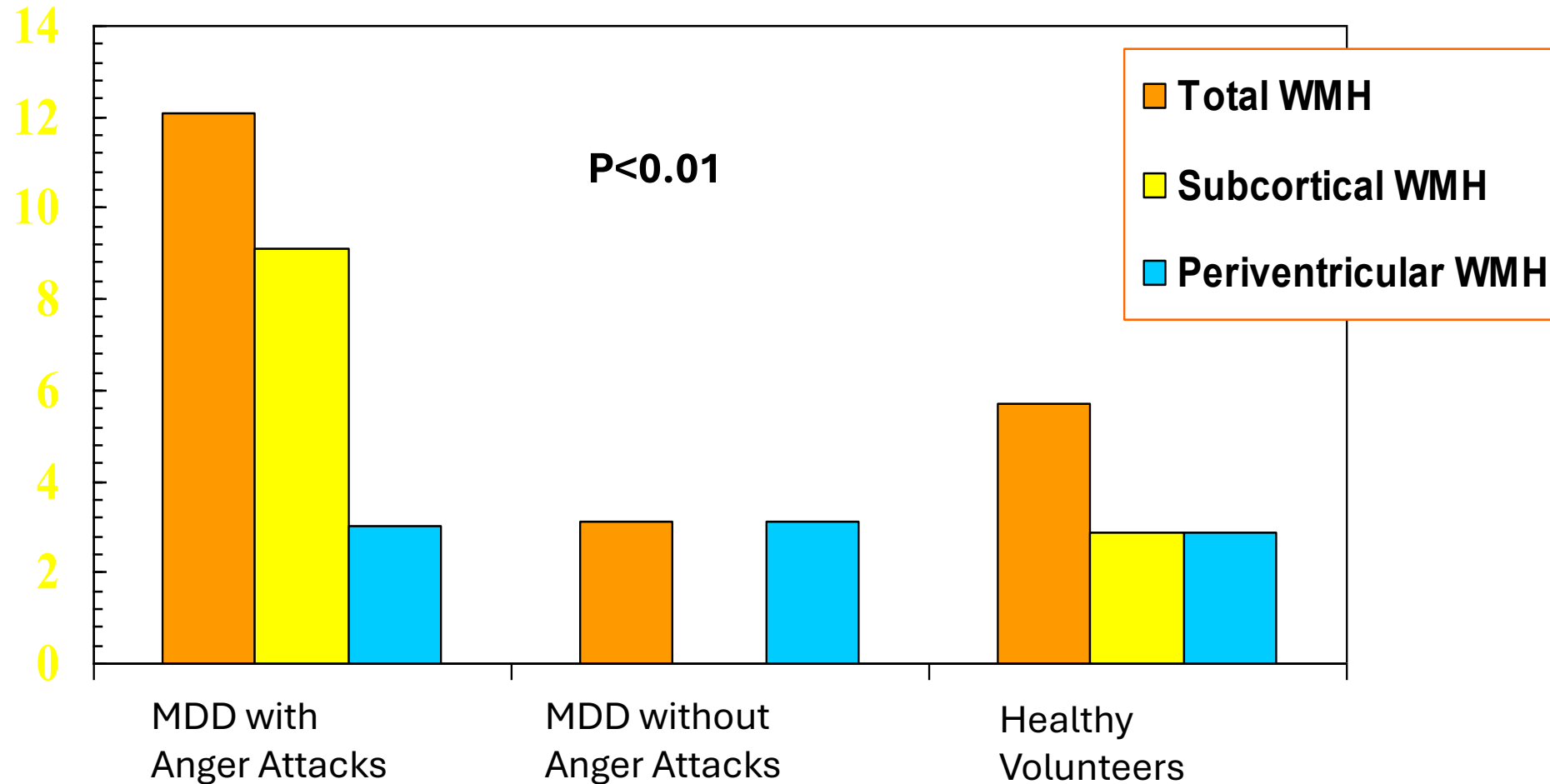
- Irritability in neurological disorders is often present, particularly when patients are depressed and/or anxious and is considered typically a symptom
- Irritability typically involves proneness to anger, aggression, and, in some cases, anger attacks
- 36% of AD patients may present with irritability (Zhao et al, J Affect Disord. 2016 Jan 15;190:264-271.)
- Post-stroke anger has a high prevalence (15-57.2%) (Ramos-Perdigues et al, Rev Neurol. 2015 Jun 1;60(11):481-9.)
- Over 50% of patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy report irritability (Bai et al, Ann Clin Transl Neurol. 2024 Nov;11(11):3010-3018)
- Generally best to avoid benzodiazepines in treating irritability as there may lead to paradoxical disinhibition

Fenfluramine-Placebo Difference in Prolactin Response in MDD with & without Anger Attacks



Fava M et al., Psychiatry Res. 2000 Apr 24;94(1):9-18

MDD with Anger Attacks is Associated with Greater Number of Brain White Matter Hyperintensities (WMH)



Iosifescu DV et al, J Nerv Ment Dis. 2007 Feb;195(2):175-8.

Psychopharmacology of Irritability

- Serotonergic medications have shown clear benefits:
 - SSRIs
 - SNRIs
 - Serotonergic TCAs such as clomipramine
 - Buspirone
- Atypical antipsychotics such as:
 - Brexpiprazole (Fava et al, J Clin Psychopharmacol. 2017 Feb 11;37(2):276–278)
 - Olanzapine (Linehan et al, J Clin Psychiatry. 2008 Jun;69(6):999-1005)
 - Risperidone (Politte & McDougale, Psychopharmacology (Berl) 2014 Mar; 231(6):1023-36)
 - Aripiprazole (Politte & McDougale, Psychopharmacology (Berl) 2014 Mar; 231(6):1023-36)
 - Lurasidone (McClennan et al, Expert Opin Investig Drugs. 2017 Aug;26(8):985-989)
 - Cariprazine (Citrome et al, J Affect Disord. 2024 Aug 1;358:353-360)
- Gabapentinoids (Thibault et al, Cardiol Young. 2024 May 3:1-7)
- Stimulants and primarily noradrenergic drugs may worsen irritability

What is Apathy?

“A lack of motivation not attributable to diminished level of consciousness, cognitive impairment, or emotional distress” (Marin, 1991)



Marin RS. Apathy: a neuropsychiatric syndrome. J Neuropsychiatry Clin Neurosci. 1991 Summer;3(3):243-54

A conceptual shift...



Lack of motivation
requires inference



Quantitative reduction of goal-directed
behaviors, despite unchanged environment or
physical constraints, that is a departure from
their previous behavioral pattern

Richard Levy, Bruno Dubois, Apathy and the Functional Anatomy of the Prefrontal Cortex–Basal Ganglia
Circuits, *Cerebral Cortex*, Volume 16, Issue 7, July 2006, Pages 916–928

Domains of Apathy

Emotional-Affective

- Inability to connect emotion with behavior and anticipate consequences thereof
- Decreased reward sensitivity and affective blunting

Cognitive

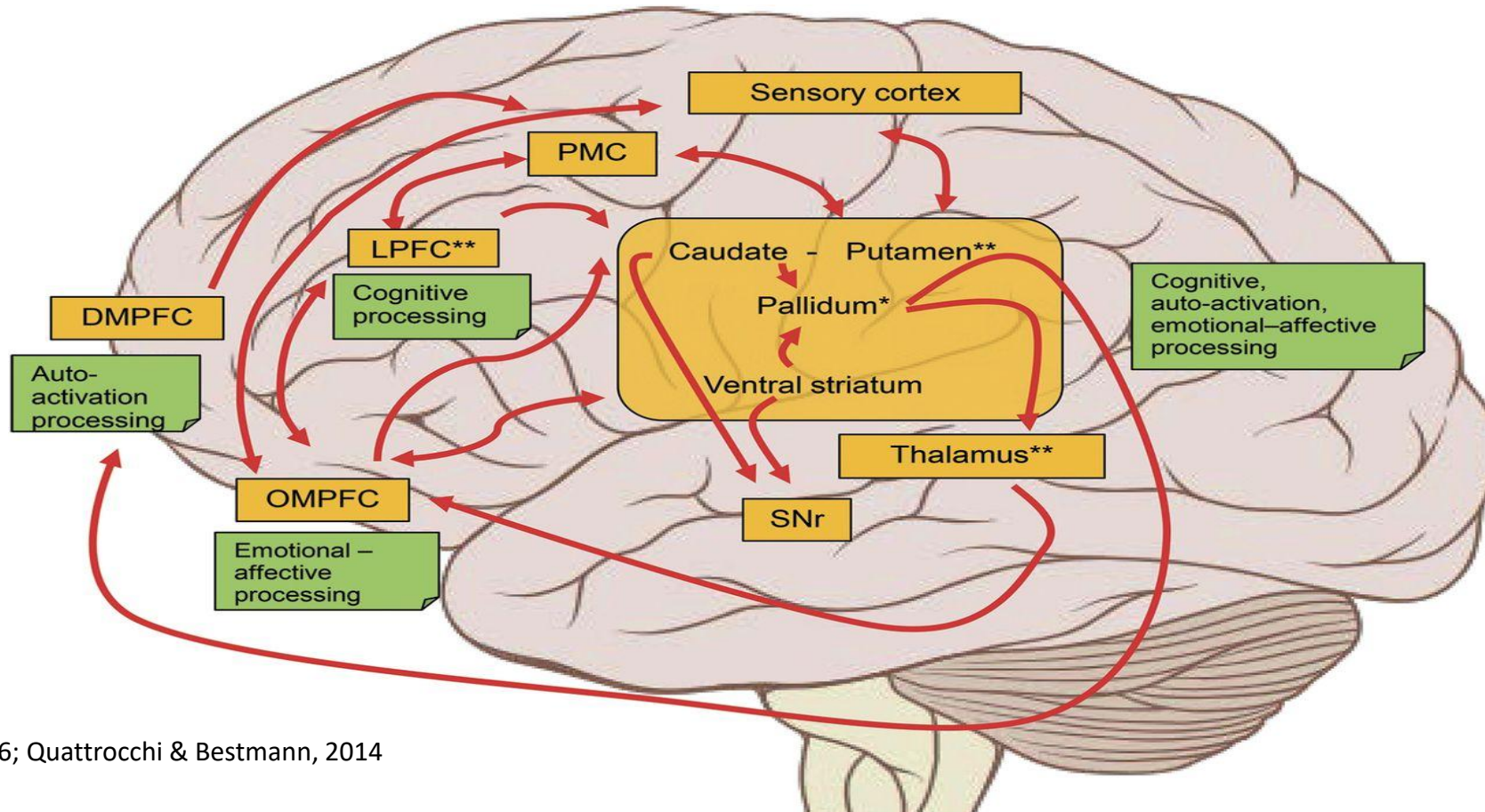
- Impaired elaboration of plans
- Executive functioning deficits

Auto-activation

- Loss of spontaneous activation
- Sensitive to external stimulation

Richard Levy, Bruno Dubois, *Cerebral Cortex*, Volume 16, Issue 7, July 2006, Pages 916–928

Pathophysiology of Apathy



Levy & Dubois, 2006; Quattrocchi & Bestmann, 2014

Apathy, Depression, or Both?

Apathy	Depression
• Reduced initiative	• Sadness
• Diminished interest in environment	• Guilt, self-denigration and/or anxiety
• Blunted emotional response, indifference, passivity, lack of anxious ruminations	• Hopelessness
• Decreased concern for others' feelings	• Pessimism
Overlapping symptoms	
• Dysphoria	
• Low social engagement	
• Decreased enthusiasm for previously enjoyable activities	

Pagonabarraga, Kulisevsky, Strafella, & Krack, 2015; Tagariello, Girardi, & Amore, 2009

Conditions Commonly Associated With Apathy

- Behavioral variant frontotemporal dementia
- Parkinson's disease
- Huntington's disease
- Progressive supranuclear palsy
- Alzheimer's disease
- Stroke
- Vascular dementia
- Traumatic brain injury
- Depression
- Schizophrenia

Apathy Impacts Clinical Outcomes and Care

- Apathy is common in MCI and predicts progression to dementia (7X increased risk)
- In dementia, apathy is typically the most common and persistent neuropsychiatric symptom
 - AD: up to 49%
 - FTD: 62 to 89%
 - LBD: 35 to 100%
- In dementia apathy is associated with increased caregiver's burden, increased functional impairment, earlier institutionalization, and costs, and increased mortality
- If identified, while no FDA approved treatments, there are interventions that can sometimes help
- Apathy may be a modifiable factor in those at risk of FTD and possibly other neurodegenerative disorders
- Apathy is associated with increased amyloid burden in mild cognitive impairment

Zhao QF, Tan L, Wang HF, Jiang T, Tan MS, Tan L, et al. The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. *J Affect Disord*. 2016;190:264–71; Mendez MF, Lauterbach EC, Sampson SM. ANPA Committee on Research. An evidence-based review of the psychopathology of frontotemporal dementia: a report of the ANPA Committee on Research. *J Neuropsychiatry Clin Neurosci*. 2008;20:130–49; Liu J, Cooper CA, Weintraub D, Dahodwala N. Pharmacological treatment of apathy in Lewy body disorders: A systematic review. *Parkinsonism Relat Disord* 2019;60:14–24; Massimo L, Evans LK. Differentiating subtypes of apathy to improve person-centered care in frontotemporal degeneration. *J Gerontol Nurs*. 2014;40:58–65; Marshall GA, Donovan NJ, Lorus N, Gidyczin CM, Maye J, Pepin LC, Becker JA, Amariglio RE, Rentz DM, Sperling RA, Johnson KA. Apathy is associated with increased amyloid burden in mild cognitive impairment. *J Neuropsychiatry Clin Neurosci*. 2013 Fall;25(4):302–7; Malpetti, M et al. Apathy in pre-symptomatic genetic frontotemporal dementia predicts cognitive decline and is driven by structural brain changes. *Alzheimer's & Dementia*; 14 Dec 2020;

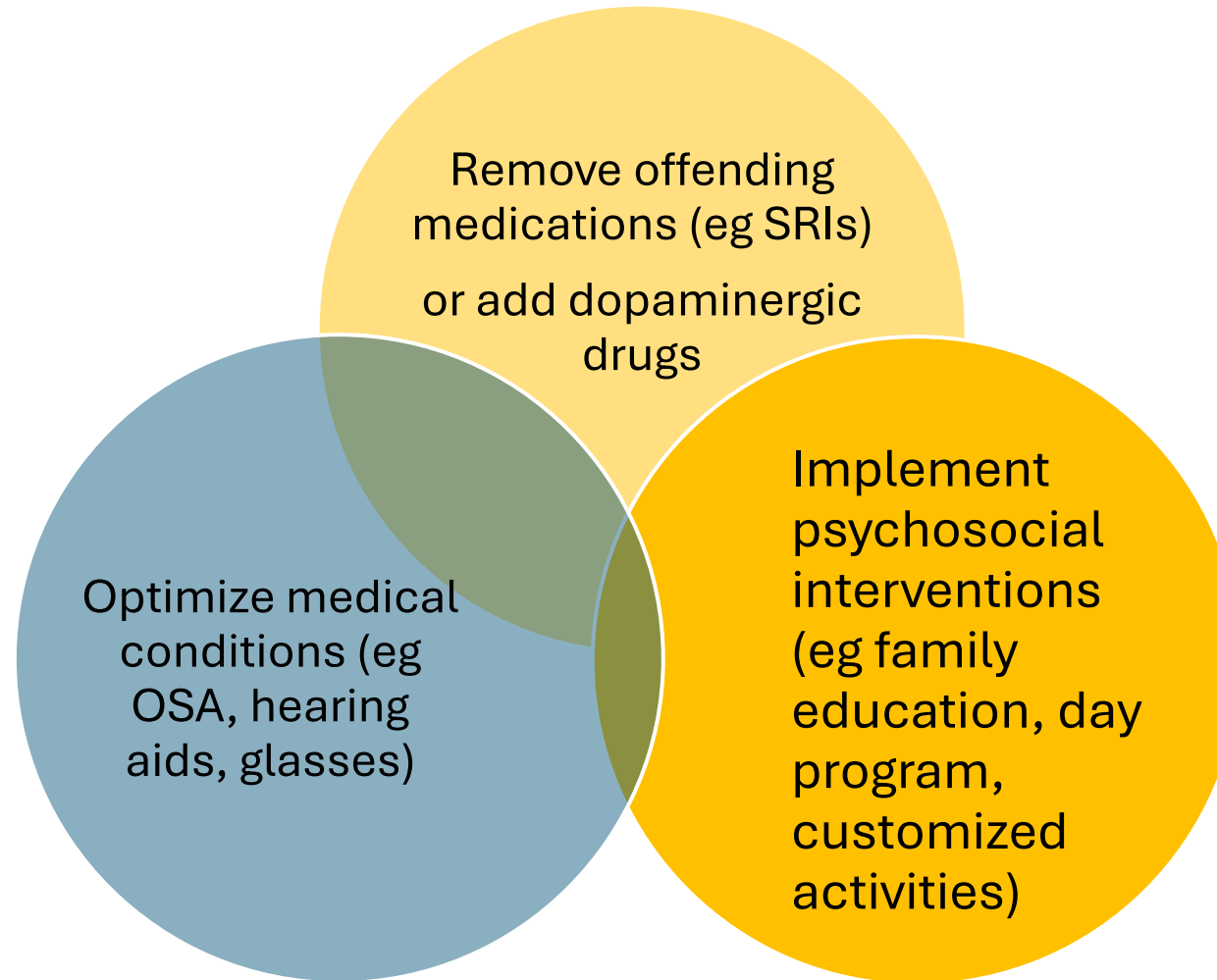
Assessments of Apathy

- Apathy Evaluation Scale (AES)
 - 18 items, can be administered by caregiver, as a self-rating, or as clinician rated semi-structured inventory
 - Excellent test/retest and interrater reliability and sensitive to change over 4 weeks
- Apathy Scale (AS)
- Apathy Inventory (AI)
- Lille Apathy Rating Scale (LARS)
- Frontal Systems Behavior Scale (FrSBe)
- Neuropsychiatric Inventory (NPI)
- Unified Parkinson's Disease Rating Scale (UPDRS)

Marin RS, Biedrzycki RC, & Firinciogullari S (1991). Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Research*, 38(2), 143–162

Lee B, Gleason C, Umucu E. Clinical utility and psychometric properties of the Apathy Evaluation Scale. *Rehabil Psychol*. 2020 Aug;65(3):311-312

Principles of Treatment of Apathy



Masdrakis VG, Markianos M, Baldwin DS. Apathy associated with antidepressant drugs: a systematic review. *Acta Neuropsychiatrica*. 2023;35(4):189-204

Pharmacotherapy of Apathy

- Acetylcholinesterase inhibitors
 - Donepezil most studied
 - No comparative data
- Memantine
 - Some evidence in AD and vascular
 - Small negative study in FTD
- Stimulants
 - Methylphenidate most studied
 - 10-20mg optimal
- Modafinil/armodafinil can improve apathy though neg trial in AD
- Bupropion negative study
- Dopamine agonists
 - Mostly studied in PD
 - Selegiline, amantadine show some promise in PD
 - In TBI related apathy, pramipexole and ropinirole were beneficial



Good review: Parrotta I et al. Prevalence, treatment, and neural correlates of apathy in different forms of dementia: a narrative review. *Neurol Sci.* 2024 Apr;45(4):1343-1376; Maier F, Spottke A, Bach JP, Bartels C, Buerger K, Dodel R, Fellgiebel A, Fliessbach K, Frölich L, Hausner L, Hellmich M, Klöppel S, Klostermann A et al. Bupropion for the Treatment of Apathy in Alzheimer Disease: A Randomized Clinical Trial. *JAMA Netw Open.* 2020 May 1;3(5):e206027

Treating Psychosis in the Context of Neurologic Illness:

General Tips

- Low-potency first-generation antipsychotics (FGAs) have very high anticholinergic activity and so best avoided given cognitive risks
- High potency FGAs and risperidone are especially apt to induce parkinsonism, with quetiapine and clozapine very unlikely to induce parkinsonian side-effects
- Pimavanserin has a unique mechanism of action devoid of anti-dopaminergic activity and is indicated for psychosis in the context of PD
- Increased mortality in the elderly Rx'd antipsychotics is a well-established risk and is a black box warning for those with dementia; it is seen with both first vs second generation agents, and is thought due to a variety of factors including possible arrhythmias and other cardiovascular issues and infectious processes
- QTc prolongation is a risk factor for potentially lethal ventricular tachyarrhythmias; highest risk is with thioridazine, IV haloperidol, droperidol, pimozide, ziprasidone, and iloperidone; lowest risk are aripiprazole and lurasidone based on current evidence (see review: Fanoe et al, *Eur Heart J*, 2014:35;1306-15)
- Antipsychotics, particularly olanzapine and clozapine significantly increase the risk for metabolic syndrome which then aggravates vascular disease and related pro-inflammatory consequences

Summary

- Neurologic and psychiatric disorders have a shared CNS substrate = much increased risk for psychiatric symptoms!
- Treating the psychiatric disorder generally improves neurologic outcomes!
- No perfect pharmacological treatment
- Always consider side-effects both to optimize adherence but also to generate the best risk: benefit equation when considering pharmacotherapy!
- Don't forget non-Rx interventions—e.g., behavioral activation, exercise, diet!
- It's not just about the patient—everyone is impacted!