March 6, 2026

Depression Update

Ways to advance your depression treatment in the primary care setting

Ryan Blum, MD
Psychiatrist, Portland VA
Director, OHSU/VA Resident Training Clinic
(Until May… then CMO at Frontier Behavioral Health, Spokane, WA)

My credentials re: Primary Care

+

My credentials re: Primary Care

Joe Blum

Paul Wellman

Dr. Joseph Blum

Veterans' Guardian Angel

During the height of 2014's CNN exposé that found dozens of army veterans died waiting for care at Veterans Affairs facilities in Phoenix, 10 area veterans paid a visit to the small Calle Real clinic to drop off cakes to show their appreciation for the care they received.

Depression

Description

- A characteristic **psychophysical state**, from **gene-environment interactions**, with changes in:

  Mood (depressed/melancholic, but also irritable, angry, apathetic, etc.) and/or interest (“**anhedonia**”)

  Psychophysical state: appetite, sleep, motor activity, cognition, negative/morbid/suicidal thoughts

- A descriptive syndrome that is **heterogeneous** in origin

- Often will present **to *you* first**, and with **physical complaints**

  11% of patients **deny psychological symptoms** altogether

Desch 2023, Lancet 2021, Simon 1999

How depression looks in primary care

Gerber 1992, Li 2023, Dahli 2021

- Fatigue (60% PPV)
- Sleep disturbance (61%),
- Nonspecific musculoskeletal complaints (43%)
- Back pain (39%)
- 3+ complaints (56%)
- Energy-related complaints (fatigue, weakness)
- Amplified/vaguely stated complaints

Depression

Genetics, cont.

Gene-Environment Interactions:

Kendler (1995) study of N=2164 twins in the Virginia Twin Registry, mean age 30.1

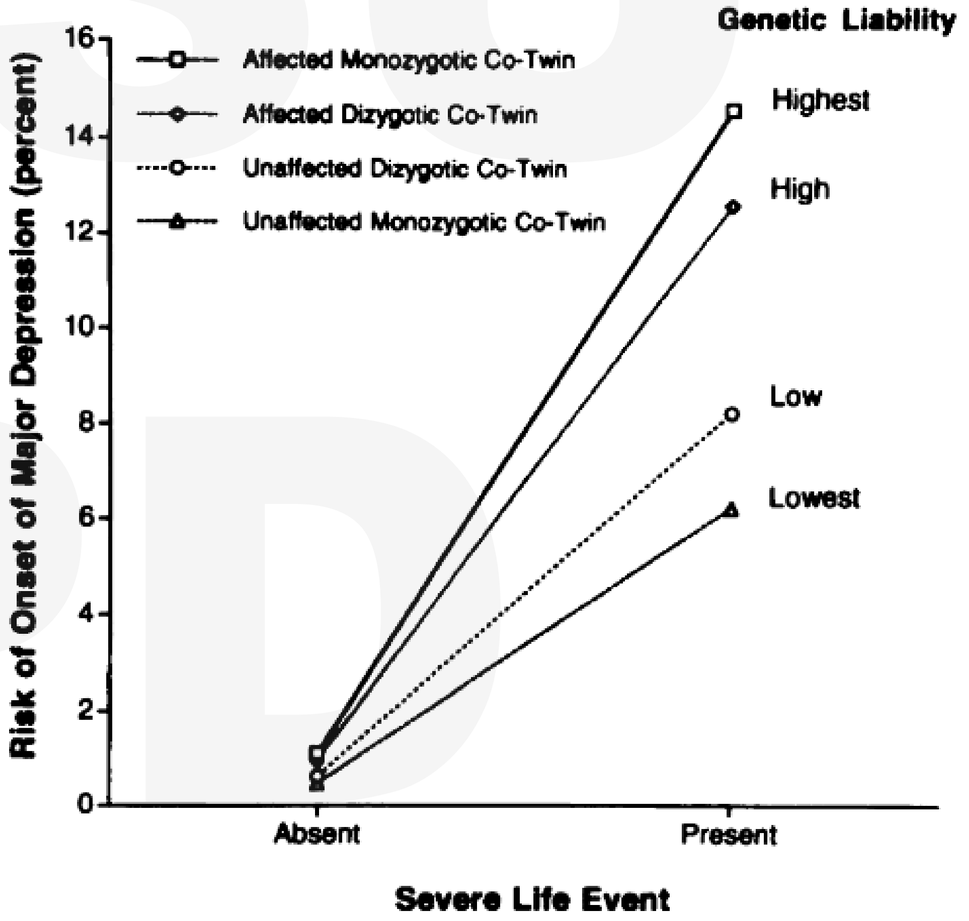
53,215 person-months and 492 MDE's

Measured *stressful life events*
(assault, marital problems, divorce, job loss, serious illness, major financial problem, being robbed, legal)

Conclusion: MDD ~ genetics + interpersonal stress

- Lowest genetic risk group:
  ~0.5% risk/mo, + stress = 6.2%
- Highest genetic risk group:
  ~ 1.1% + stress = 14.6%

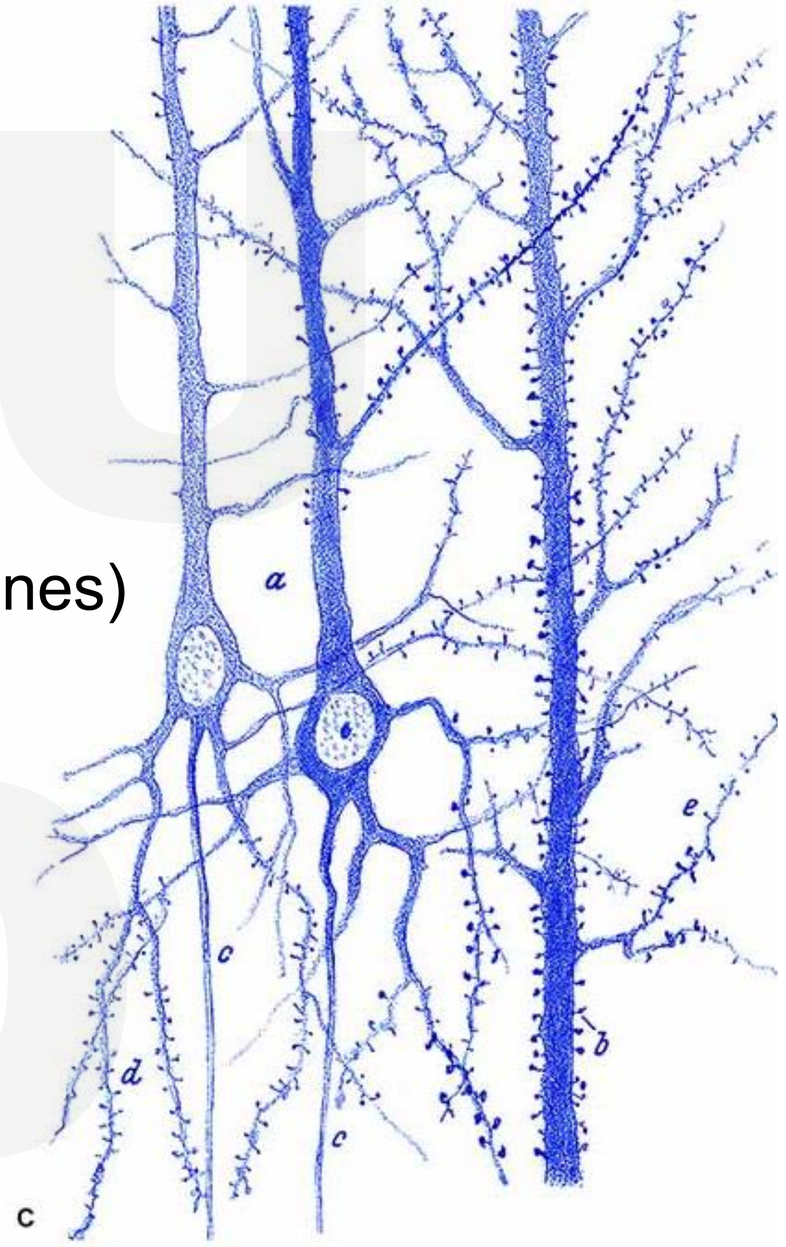
FIGURE 1. Risk of Onset of Major Depression per Person-Month as a Function of Genetic Liability and the Presence or Absence of a Severe Stressful Life Event in That Month Among 2,060 Female Twins[a]



Depression

Biological theories have evolved over time

- Monoamine hypothesis (“chemical imbalance”)
- Dysregulated stress response
  (HPA axis, excess glucocorticoids, inflammatory cytokines)
- Inflammation
- Disorder of synaptogenesis
  (Reduced BDNF and ohter neurotrophins)
- Inhibitory circuit dysfunction
  (GABAergic, glutamatergic system derangement)



Depression

Prevalence, global impact

- A problem that is **common**, and **cross-cultural**:

  21m (8.4 %) US adults & 4m (17.0 %) US adolescents experienced a MDE in 2020

- **3rd largest cause of YLD** in the world (HA, back pain) in 2017 (+28% in COVID)
- Lifetime prevalence ~20%

  Often MDD starts in teens/20's, and greatly impacts function over lifecycle

- Associated w/ DM, HTN, CAD, stroke, cancer, obesity

  Estimated contribution to **all-cause** mortality is 10% (!)

- **Adequate evidence based-treatment is effective** and yet far, far too **scarce**

Depression Treatment

“Psychiatric Management” per APA Practice Guideline (2010)

- “…a broad array of interventions and activities that psychiatrists should initiate and continue to provide to patients with major depressive disorder through all phases of treatment”

1. Estab./maintain **therapeutic alliance**
2. Complete a **psychiatric assessment**
3. **Identify comorbidities**
4. Develop a **treatment plan**
5. **Evaluate safety** of the patient
6. Establish the **appropriate setting**
7. **Coordinate care** w/ other clinicians
8. **Monitor status**, integrate measures
9. **Enhance adherence** throughout
10. Provide **psychoeducation**

Depression Treatment

“Psychiatric Management” per APA Practice Guideline (2010)

- “…a broad array of interventions and activities that psychiatrists should initiate and continue to provide to patients with major depressive disorder through all phases of treatment”

1. Estab./maintain **therapeutic alliance**
2. Complete a **psychiatric assessment**
3. **Identify comorbidities**
4. Develop a **treatment plan**
5. **Evaluate safety** of the patient
6. Establish the **appropriate setting**
7. **Coordinate care** w/ other clinicians
8. **Monitor status**, integrate measures
9. **Enhance adherence** throughout
10. Provide **psychoeducation**

AGENDA

Focus on Therapeutic Alliance

Master starting and stopping antidepressants

Identify and treat comobidities

Review the “atypical antidepressants” (bupropion, mirtaz., etc.)

Demystify augmentation: light, exercise, supplements, thyroid, atypicals

Introduce newer treatments (ketamine, neurosteroids, TMS, psilocybin)

Therapeutic alliance

Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

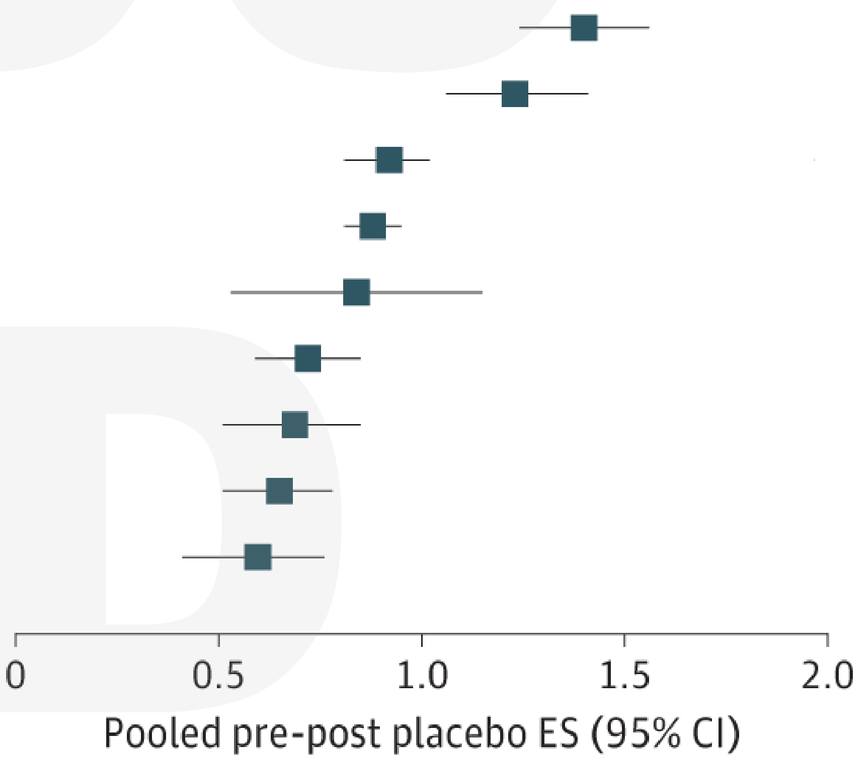
Andrea Cipriani, Toshi A Furukawa, Georgia Salanti*, Anna Chaimani, Lauren Z Atkinson, Yusuke Ogawa, Stefan Leucht, Henricus G Ruhe,*

oa

Placebo Effect: By Diagnosis

Diagnosis	Study participants, No.	Q	I^2, %	ES (95% CI)
MDD	1598	47.9	81	1.40 (1.24-1.56)
GAD	1457	61.4	85	1.23 (1.06-1.41)
Panic disorder	1307	20.8	57	0.92 (0.81-1.02)
ADHD	1189	7.3	0	0.88 (0.81-0.95)
PTSD	655	99.8	91	0.84 (0.53-1.15)
Social phobia	1180	34.7	74	0.72 (0.59-0.85)
Mania	967	53.1	83	0.68 (0.51-0.85)
OCD	819	29.6	70	0.65 (0.51-0.78)
Schizophrenia	888	50.0	82	0.59 (0.41-0.76)

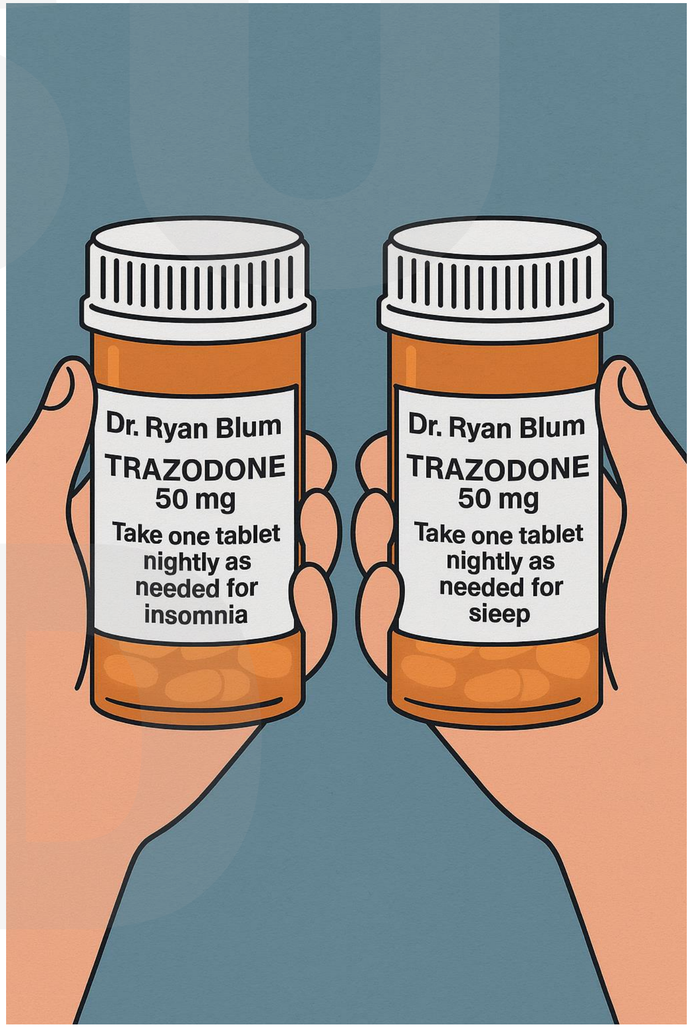
Heterogeneity: $\chi^8_2 = 88.50$ ($P < .01$)



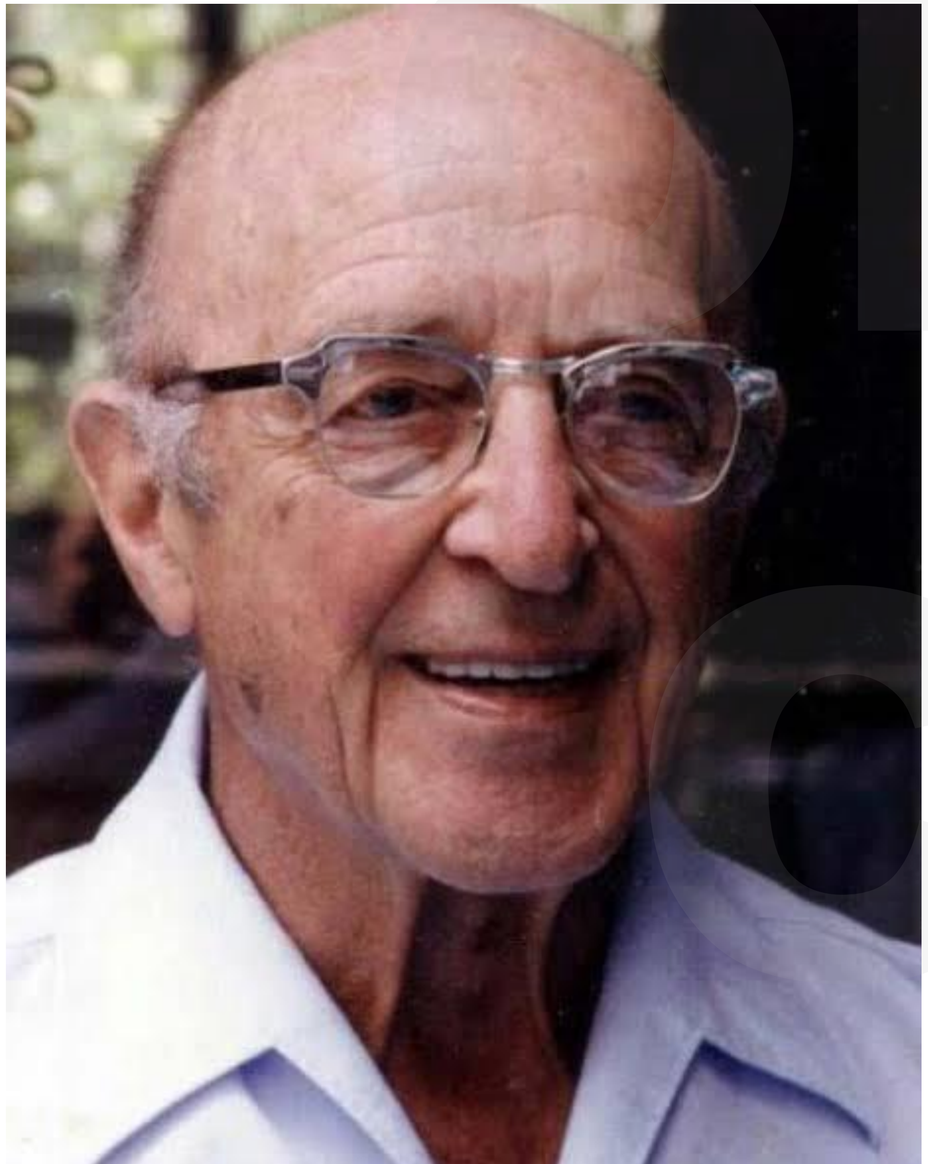
Bschoro, et al Jama Psychiatry 2024

Placebo effect: Patient & Provider

- Patient Contributions
  - Natural history of the disease
  - Expectations
  - Conditioning/prior experiences
  - Hawthorne effect (awareness of being observed)
  - Personality traits
- Provider Contributions
  - Empathy
  - Warmth
  - Competence
  - Communication skills

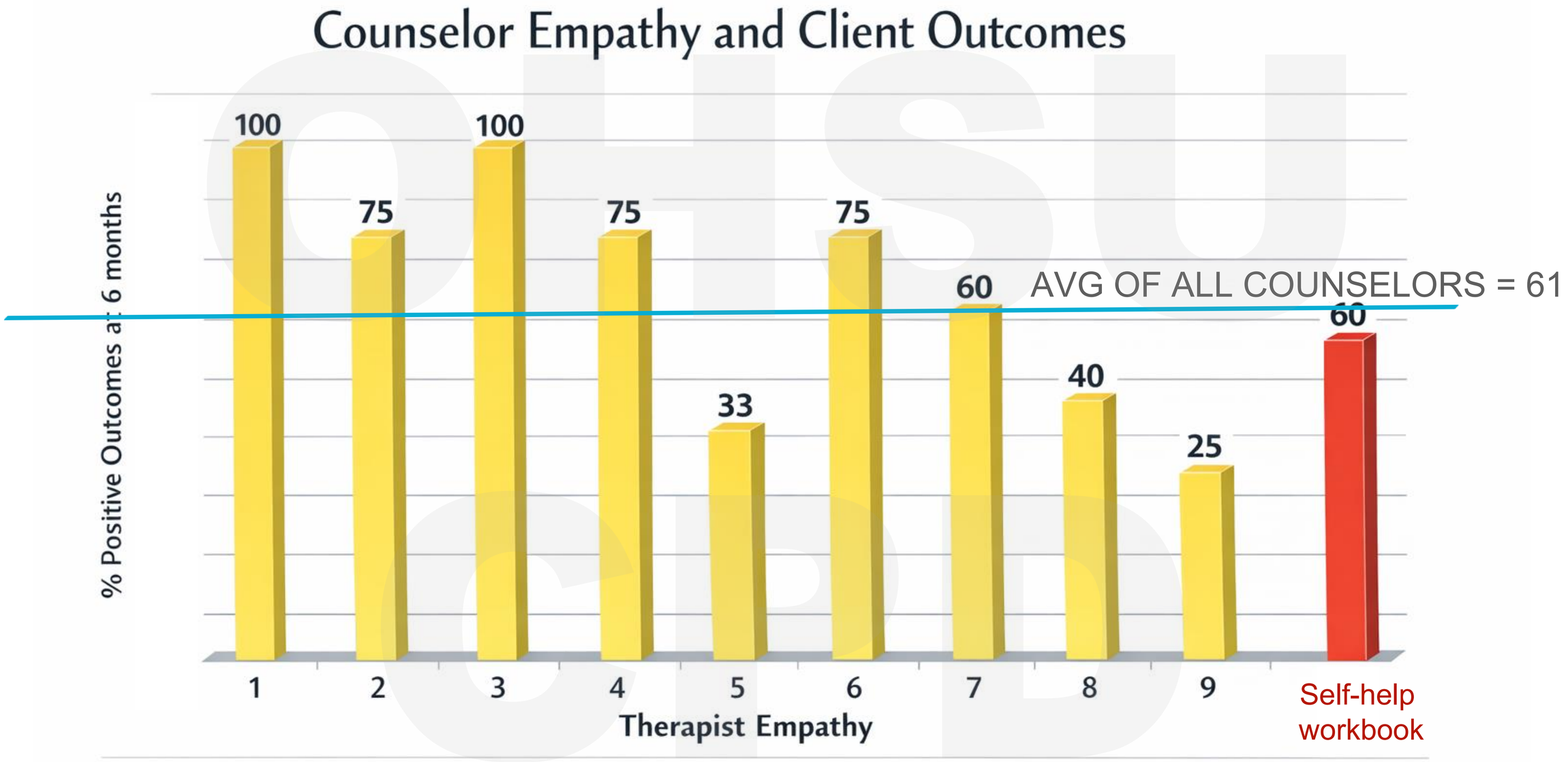


Improving your placebo



Carl Rogers (1902-87)

Empathy
Acceptance
Congruence



Miller, W. R., Taylor, C. A., & West, J. (1980). *Focused versus broad-spectrum behavior therapy for problem drinkers.* *Journal of Consulting and Clinical Psychology*, 48(5), 590–601.

Motivational Interviewing!

- Evidence-based way to enhance care, may prevent burnout
- Teachable with simple structured feedback

- **Spirit**
  - Partnership
  - Acceptance
  - Compassion
  - Evocation
- **Skills** (OARS+I)
  - Open-ended questions
  - Affirmations
  - Reflective Statements
  - Summaries
  - (providing Information)

AGENDA

Focus on Therapeutic Alliance

Master starting and stopping antidepressants

Identify and treat comobidities

Review the “atypical antidepressants” (bupropion, mirtaz., etc.)

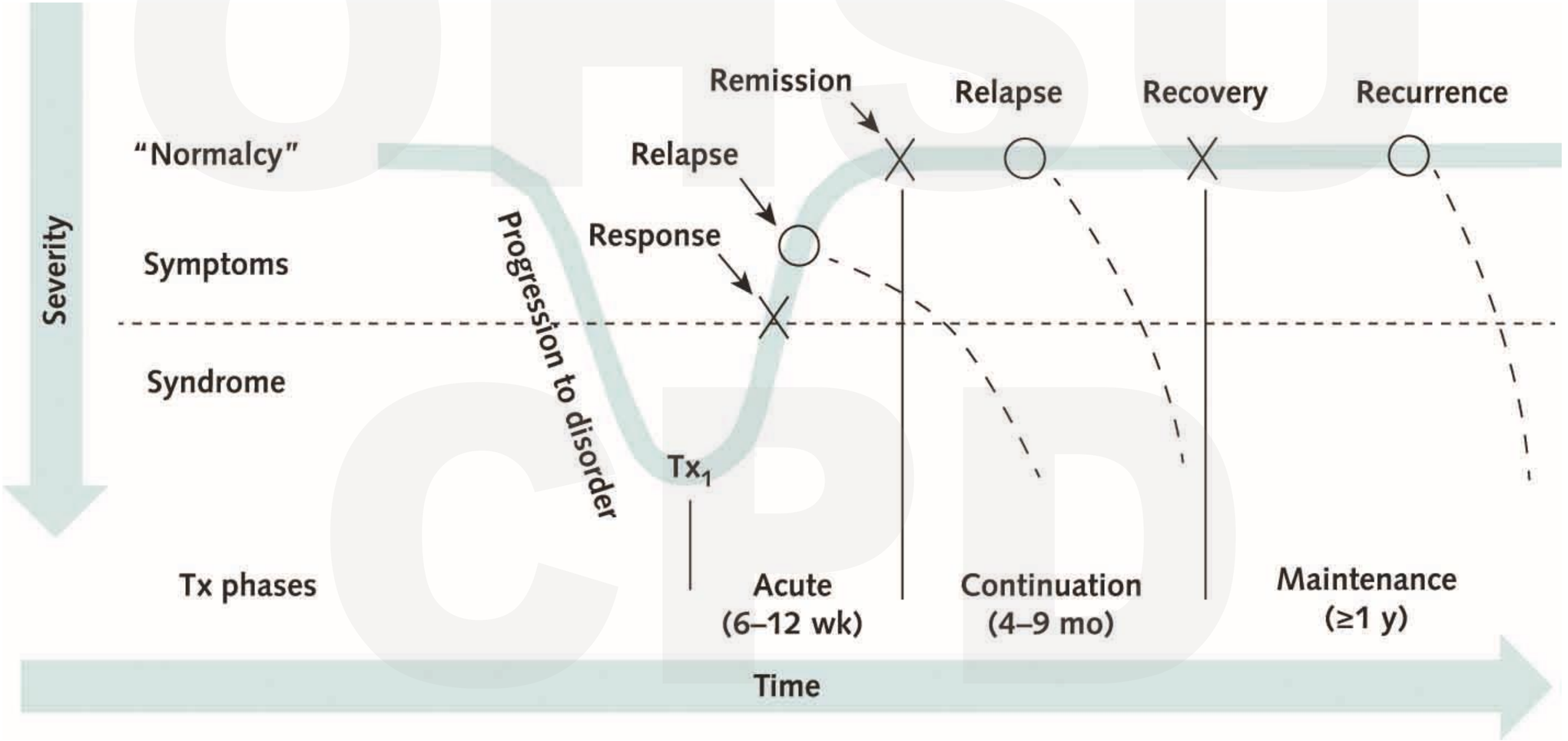
Demystify augmentation: light, exercise, supplements, thyroid, atypicals

Introduce newer treatments (ketamine, neurosteroids, TMS, psilocybin)

Master Starting/Stopping

Depression Treatment

Concepts: Treatment Phases



Starting antidepressants

Strategies, cont.

- **Start low, go slow** for (almost) everyone
- Start especially slow for the **elderly** and those with **high anxiety**
- Don't be afraid of PRN's for anxiety in the first 1-2 mo

  — e.g. lorazepam 0.5-1mg twice daily as needed for anxiety

  — **Set expectations** for short-term/occasional use from the start
- Aim for target doses of ~20-40 fluoxetine equivalents

  — Minimal additional benefit at higher doses

Fluoxetine equivalents

	Bollini et al. (32)	Hayasaka et al. (31)	Jakubovski et al. (33)	WHO (34)
Citalopram	30	NR	33.3	20
Clomipramine	100	58	NR	100
Escitalopram	NR	9	16.7	10
Fluoxetine	20	20	20	20
Fluvoxamine	100	72	100	100
Paroxetine	20	17	20	20
Sertraline	83	49.3	120	50

These doses were calculated based on fluoxetine equivalents of serotonin reuptake inhibitors (SRIs) used in previous meta-analytic studies of antidepressants and according to the American Psychiatric Association dose recommendations for individual SRIs in obsessive–compulsive disorder (OCD). NR, none reported.

Xu et al 2021

Starting antidepressants

Strategies, cont.

- Watch for certain ***serious but uncommon ADR's***:

  — Treatment-emergent **SI, hypomania/mania**

  — **hyponatremia** (highest risk: > 80 years old, F > M, CKD, on Na wasting Rx)

- Utilize Measurement-Based Care (e.g. PHQ, Geriatric Depression Scale) ~ outcomes by 50%! (Fortney 2017)

- **Follow up** within 2-6 weeks**, earlier if unstable;**

  — Utilize **collaborative care programs** w/ care coord./nurse care mgrs. to monitor & intervene

Depression Treatment

Relapse Prevention

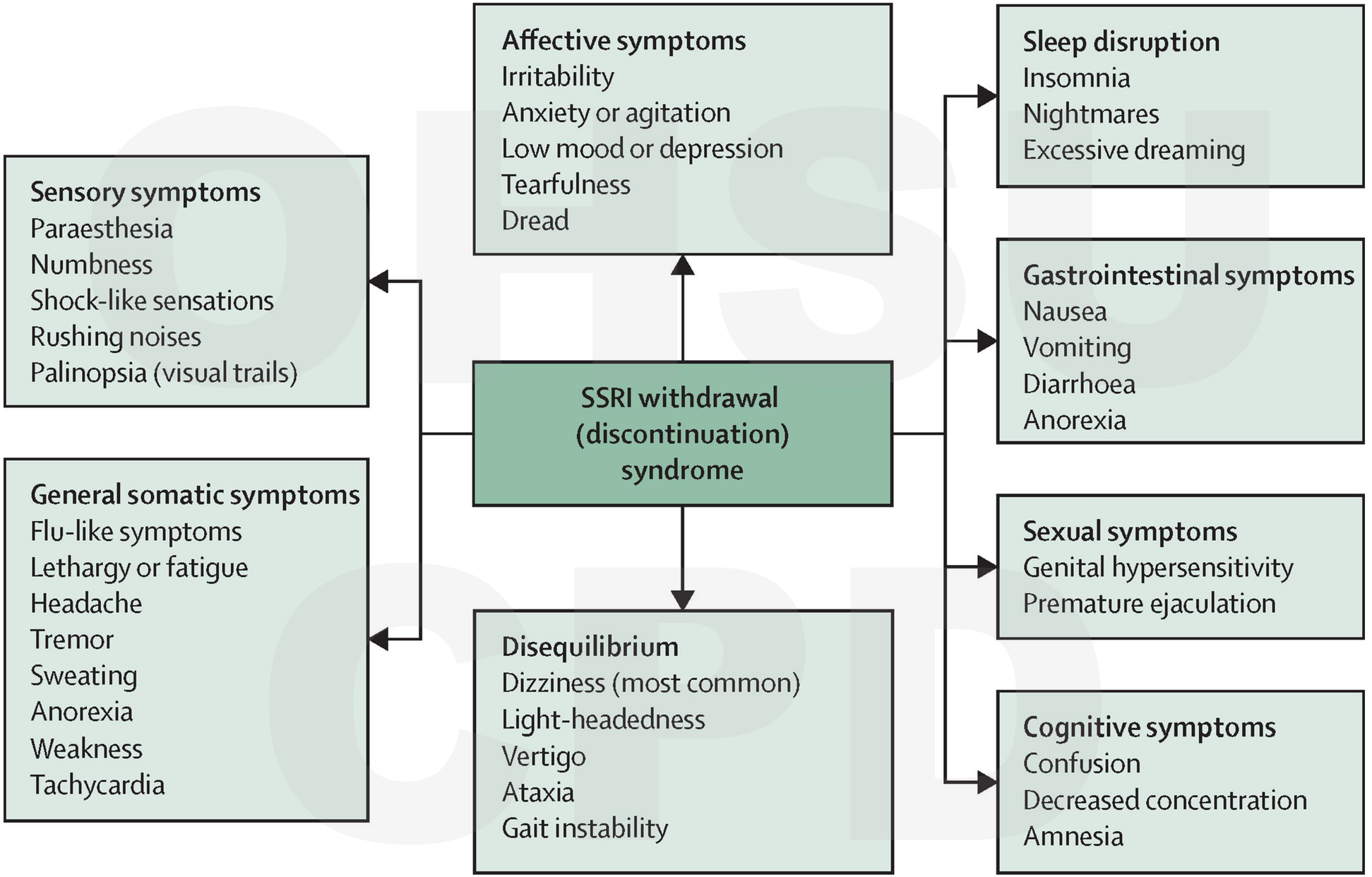
- Medications:
  - **Continuing antidepressants reduced relapse by 70%** x up to 36 mo
  - 6 mo relapse rate is ~41% per VA guidelines (2022)
  - In 72 trials (n=14450) x 36 weeks, ADs > placebo RR 1.9, NNT=4
  - **Longer duration of Rx treatment does not reduce relapse after withdrawal!**
  - Guidelines recommend 6-12 mo or indefinitely after 3+ episodes
  - However, **adherence to this guideline is low**

- Other interventions:
  - Strong evidence for psychotherapy during continuation phase (21-31% in RCTs of CBT and MBCT)
  - Neurostimulation has less evidence but effect suggestive of benefit

Discontinuation Syndrome

- Anxiety, insomnia, irritability, mood lability, flulike symptoms
- “Brain zaps” = sensation of shooting electrical impulses
- Rates are ~15% (placebo control) or up to 31% without control
- Severe discotinuation ~1/35 patients (Henssler 2024)

  12% of those on imipramine, 5% parox, 6% venlafax/desvenlafax
- Short 1/2 life is worse (venlafaxine, duloxetine, paroxetine)
- Long 1/2 life (fluoxetine) is least likely, but not impossible



Horowitz and Taylor 2019

Discontinuation & the "hyperbolic taper"

Citalopram dose (mg)	SERT occupancy (%)
60·0	87·8%
40·0	85·9%
20·0	80·5%
19·0	80·0%
9·1	70·0%
5·4	60·0%
3·4	50·0%
2·3	40·0%
1·5	30·0%
0·8	20·0%
0·37	10·0%

SERT occupancy was calculated using the Michaelis-Menten equation of best fit derived by Meyer and colleagues.[60] Common clinical doses and doses corresponding to 10% decrements of SERT inhibition are displayed. These doses could be produced by a combination of tablets and liquid formulations. Approximations might be necessary. SERT=serotonin transporter.

Table 2: **Derivation of SERT occupancy from citalopram dose using the Michaelis-Menten equation of best fit**

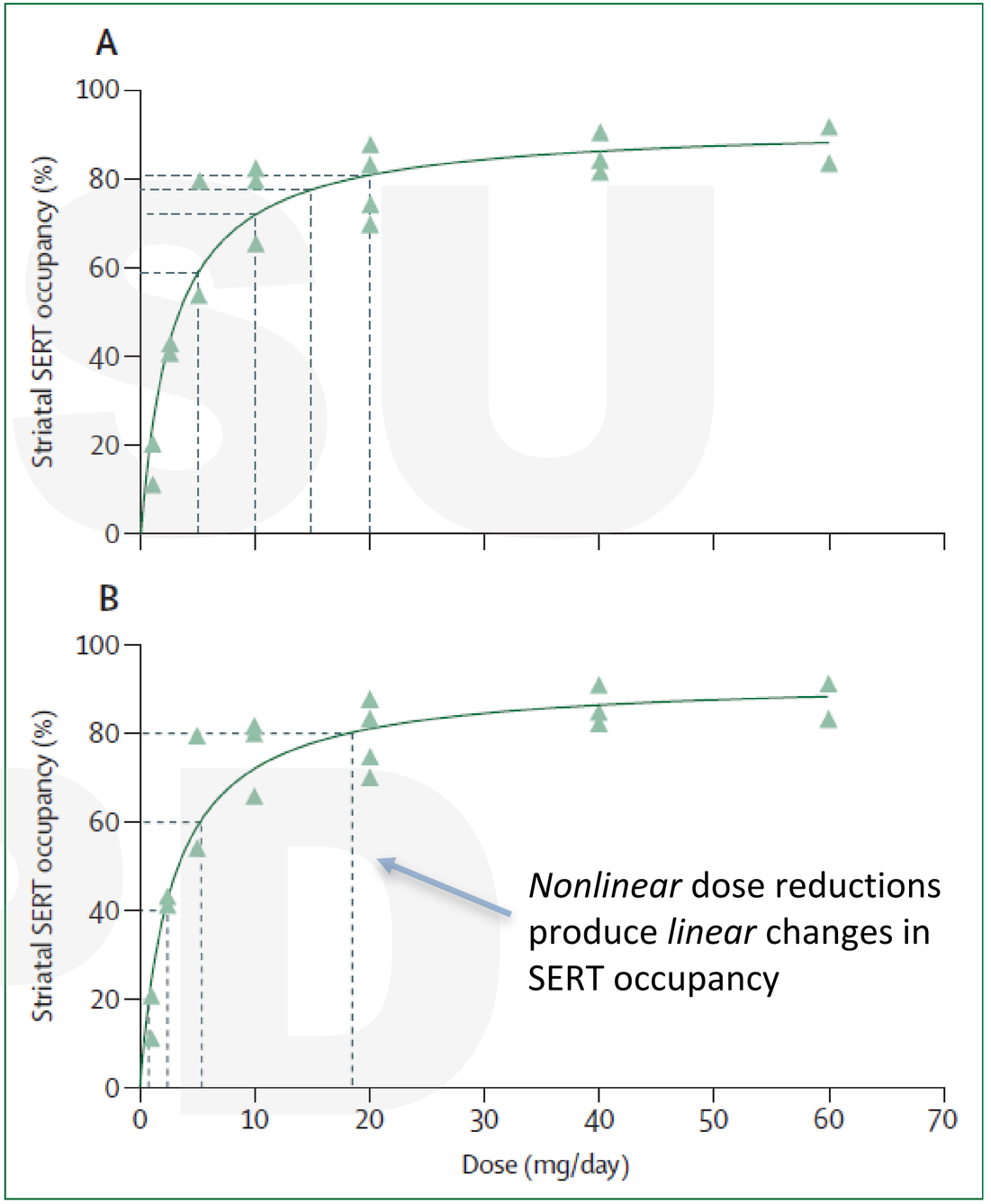


Figure 4: **Effect of linear and hyperbolic citalopram dose reductions on SERT occupancy**

Horowitz and Taylor 2019

Preventing discontinuation

Practical advice

- **Taper by <20% each step**, and **slower at the end** (i.e. in lower dose range)
- Longer duration of treatment ~ longer taper (e.g. 1 year/1mo, 10 yrs/6-12 mo)
- **Monitor** for discontinuation and **slow down or reverse course** if needed
- **Switch to fluoxetine** & let it self-taper (e.g. 20mg x 1-7 days)
- Reserve liquid formulations/compounding for rare/difficult cases
  - — SSRI's in **liquid form** incl. sertraline, citalopram, fluoxetine, paroxetine
  - — Others (e.g. venlafaxine) can be **compounded**

AGENDA

Focus on Therapeutic Alliance

Master starting and stopping antidepressants

Identify and treat comobidities

Review the “atypical antidepressants” (bupropion, mirtaz., etc.)

Demystify augmentation: light, exercise, supplements, thyroid, atypicals

Introduce newer treatments (ketamine, neurosteroids, TMS, psilocybin)

Comoribidities

Comorbidities

In Primary Care setting

Incomplete remission is often due to unaddressed comorbidities!

- **Anxiety disorders (overall): 53–57%**
  - **Generalized anxiety disorder: 20–21%**
  - **Social anxiety disorder: 29%**
  - **Panic disorder: 7–11%**
  - **Agoraphobia: 5–9%**
- **PTSD: 4–19%**
- **OCD: 5–13%**
- Sleep disorders (primarily insomnia): 51%
- Substance use disorders:
  Alcohol abuse/dependence: 12%
  Drug abuse/dependence: 7%
  Nicotine dependence: 27–38%
- Dysthymia (persistent depressive disorder): 20%
- Eating disorders: Bulimia: 12%, anorexia nervosa: less common

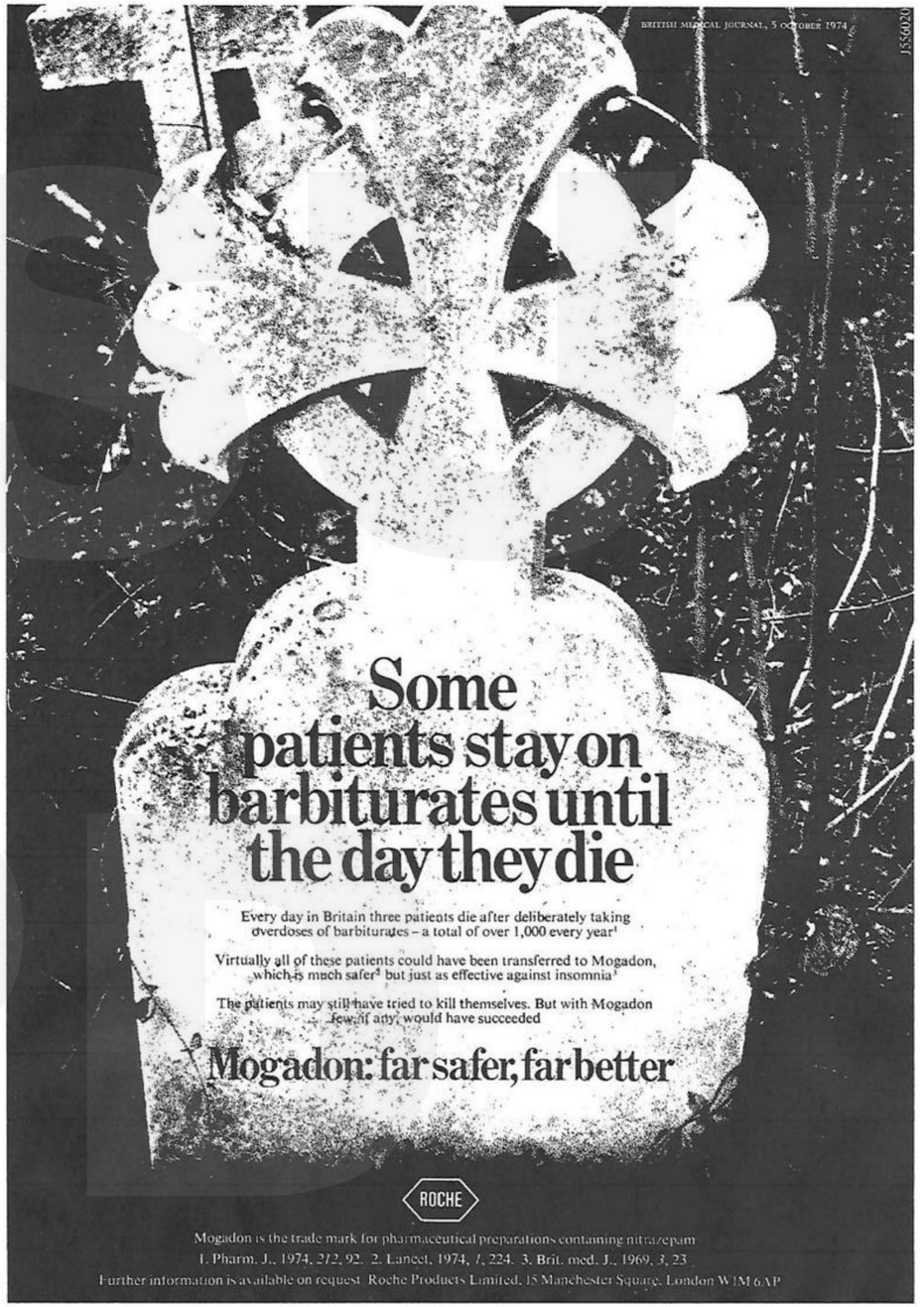
Latas 2024, Rush 2005, Zimmermann 2002, Thaipisuttikul 2014

Medications for anxiety

- (Antidepressants: Reuptake inhibitors, tricyclics, MAO inhibitors_
- Benzodiazepines
- Buspirone
- Gabapentin and pregabalin
- Antihistamines
- (Atypical antipsychotics)
- Adrenergic agents (propranolol, clonidine)

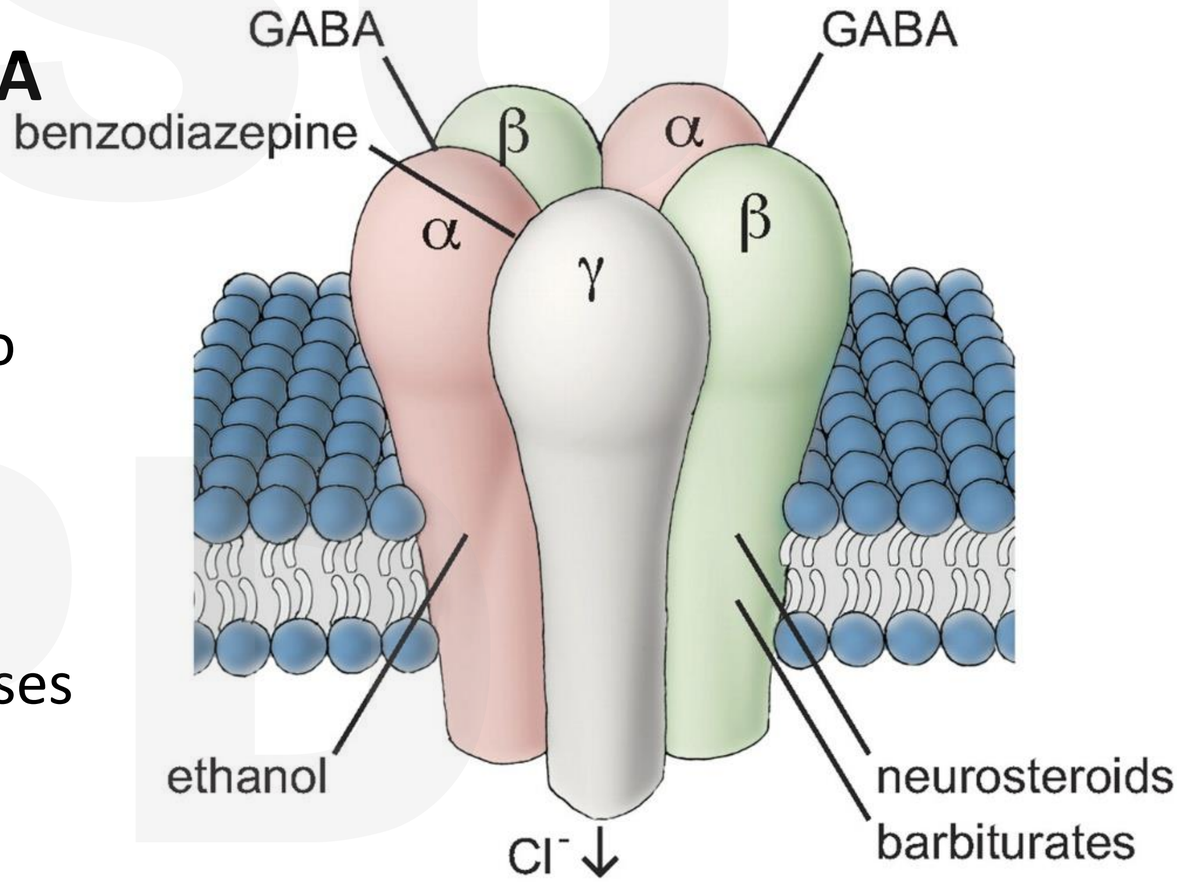
Benzodiazepines

- Discovered in 1955 (chlordiazepoxide)
- Introd. 1960's as safter alt's to barbiturates
- **Highly effective** and prone to problems
  - Tolerance/dependence, misuse/addiction
- Critical for many problems:
  - Anxiety Disorders
  - Alcohol withdrawal
  - Acute agitation
  - Insomnia
  - Seizure control
  - Procedural sedation and anesthesia
- Overprescribed?
  - 1/25 US adults in 2021 (!) had Rx



Benzodiazepines – Mechanism of Action

- All act on Benzodiazepine Receptor (BZ-R)
- BZ-R = allosteric mod. site on **GABA-A**
  - GABA-A = ionotropic, ion ligand-gated (B is metabotropic, GPCR)
  - Heteromer w/ multiple subunits, leading to many possible config.'s
  - 19 genes clustered on chromosome 5
  - Bzd binds at alpha-gamma, causes **confirmational change**, Cl- goes in, depresses cell electrical activity



Benzodiazepine Adverse Effect

- **Sedation**
- **Impaired cognition, psychomotor skills**
- **Memory impairment**
- **Disinhibition**
- **Rebound anxiety**
- **Misuse and addiction**
- **Dependence**
- **Withdrawal**
  - Symptoms include: tachycardia, increased blood pressure, muscle cramps, anxiety, insomnia, panic attacks, impairment of memory and concentration, perceptual disturbances, derealization, hallucinations, hyperpyrexia, seizures

Benzodiazepine withdrawal

- Can be life threatening, require longer tapers than alcohol
- Taper slowly, and over time proportional to duration of Tx
  - See the *Ashton Manual*
- Change short-acting (e.g. alpraz) to longer (e.g. clonaz, diaz)
- Tapering too fast can increase risk of overdose, etc.
- Plan for additional psychosocial support during taper
- Consider adjunctive Rx, including:
  - Valproic acid
  - Oxcarbazepam

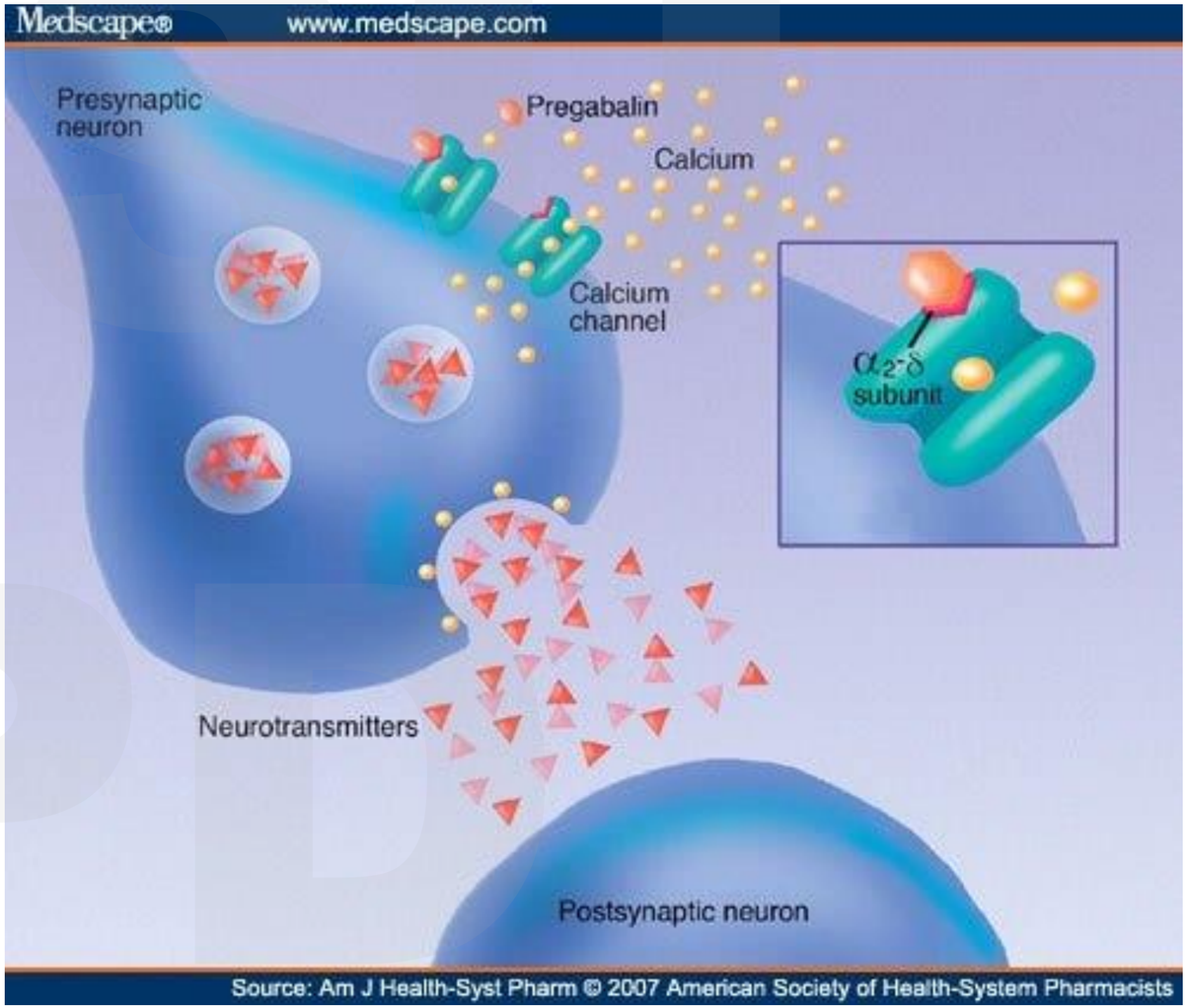
Buspirone

- 5HT-1A agonist
- Monotherapy or augmentation strategy
- Non-addictive
- Slow to work, like antidepressants
  - Less immediately gratifying c/w bzd
- Needs to be taken 2-3 times daily, not as needed
- ADR's are minimal, but include:
  - Nausea, headache, insomnia, restlessness, dizziness

Gabapentin and pregabalin

- GABA analogues which bind a-2-delta subunit of V-gated Ca channels
- Quick onset (within days)
- Both also effective for chronic pain
- Gabapentin is less addictive

- ADR's include:
  - Sedation, dizziness
  - Rebound anxiety, even seizure
  - Weight gain, sexual dysfunction
  - Peripheral edema



Antihistamines

- Hydroxyzine
  - Sedating antihistamine (H1 antagonist)
  - Use: best short-term, as needed
  - Common adverse effects:
    - dry mouth, sedation
  - Worry about long-term cognitive impairment

Adrenergic agents

- β-blockers, e.g *propranolol*
  - First line for performance anxiety
    - AKA “Social Anxiety, Performance-Type” in DSM5
  - Help (mainly) peripherally with palpitations, shaking hands, etc.
- *Prazosin*
  - α-1 antagonist
  - Useful in PTSD-related nightmares/insomnia
  - Doses 1-12+mg, typically underdosed in practice
  - Major problem is orthostatic hypotension
- *Clonidine*
  - Brainstem α-2 agonist, which activates inhibitory neurons -> CNS depression
  - Useful in PTSD, opioid withdrawal
  - Clonidine has efficacy in ADHD (via post-synaptic α-2?), as does *guanfacine (*α-2a agonist)

PTSD

- **Not all trauma leads to PTSD,** but PTSD must involve **Criterion A** trauma
- 1+ mo of **intrusion**, **avoidance**, **neg. mood/cog**, and **arousal/reactivity** Sx
- **Treatment:**
  - Antidepressants help with the **hypervigilance** symptoms
  - **Prazosin** 1-20mg (start 1, increase by 1 to 5mg to start) for NM's
  - Or **clonidine** 0.1-0.4mg nightly or twice daily for anxiety/sleep
  - **Psychotherapy** is key to address avoidance, guilt/shame, etc.
  - **Evidence-based therapies** include CPT, PE, EMDR, etc.

OCD

- Assess using YBOCS
- **Antidepressants are 1st line**, and sometimes need dosing >> MDD
- **Recommend** exposure-based psychotherapies, e.g. ERPT
- **Augment** with buspirone, aripiprazole, ondansetron, etc
- See **International OCD Foundation**, or **NOCD** online specialty treatment

Optimal dosing in OCD

SRI	Minimum (mg/day)	Maximum (mg/day)	Occasionally prescribed maximum dose (mg/day)[a]
Citalopram	20	80	120
Clomipramine	25	250	[b]
Escitalopram	10	40	60
Fluoxetine	20	80	120
Fluvoxamine	50	300	400
Paroxetine	20	60	100
Sertraline	50	200	400

[a] *These doses are sometimes used for patients who were rapid metabolizers or with no/mild side effects and inadequate therapeutic response after 8 weeks or more at the usual maximum dose.*

[b] *Combined plasma levels of clomipramine plus desmethylclomipramine 12 h after the dose should be kept below 500 ng/ml to minimize risk of seizures and cardiac conduction delay.*

Xu et al 2021

Alcohol Use Disorder

MI + Pharmacotherapy

- MI decreases problem drinking, esp. binge drinking
- Phamarcotherapy is effective

First-Line (FDA-Approved)

Medication	Typical Dose	When to Use	Key Cautions
Naltrexone (oral)	50 mg daily (start 25 mg)	Reduce heavy drinking or maintain abstinence	Avoid with opioids; caution severe liver disease
Naltrexone (IM)	380 mg IM monthly	Adherence issues; same indications as oral	No opioids; injection reactions
Acamprosate	666 mg TID (333 mg TID if CrCl 30–50)	Maintain abstinence	Contraindicated CrCl <30
Disulfiram	250 mg daily (max 500 mg)	Abstinence when supervised	Avoid active drinking, psychosis, severe cardiac disease

Second-Line / Off-Label (Evidence-Supported)

Medication	Typical Dose	When to Consider	Key Cautions
Gabapentin	Titrate to 600 mg TID (max 3600 mg/day)	Withdrawal symptoms, insomnia, anxiety	Sedation; renal dosing
Topiramate	Start 25 mg daily → up to 300 mg/day	Reduce heavy drinking	Cognitive effects, paresthesias
Baclofen	15–80 mg/day divided	Cirrhosis; relapse prevention	Sedation; renal caution
Varenicline	0.5 mg daily → 1 mg BID	Dual tobacco + alcohol use	Nausea, vivid dreams

Rehm 2025, APA Guideline 2018, VA/DOD 2022

AGENDA

Focus on Therapeutic Alliance

Master starting and stopping antidepressants

Identify and treat comobidities

Review the “atypical antidepressants” (bupropion, mirtaz., etc.)

Demystify augmentation: light, exercise, supplements, thyroid, atypicals

Introduce newer treatments (ketamine, neurosteroids, TMS, psilocybin)

AGENDA

Focus on Therapeutic Alliance

Master starting and stopping antidepressants

Identify and treat comobidities

Review the “atypical antidepressants” (bupropion, mirtaz., etc.)

Demystify augmentation: light, exercise, supplements, thyroid, atypicals

Introduce newer treatments (ketamine, neurosteroids, TMS, psilocybin)

AGENDA

Focus on Therapeutic Alliance

Master starting and stopping antidepressants

Identify and treat comobidities

Review the “atypical antidepressants” (bupropion, mirtaz., etc.)

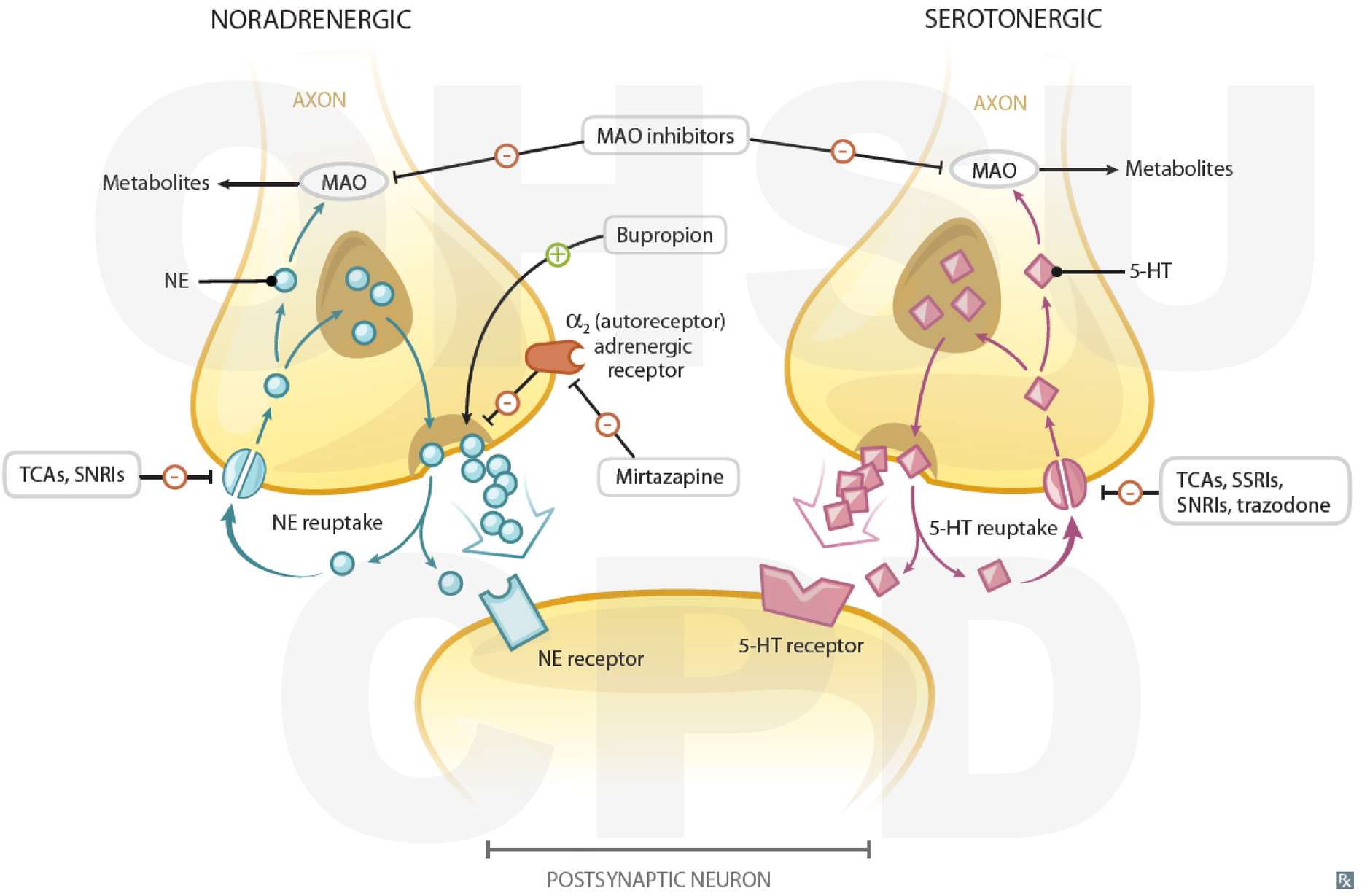
Demystify augmentation: light, exercise, supplements, thyroid, atypicals

Introduce newer treatments (ketamine, neurosteroids, TMS, psilocybin)

“Atypical” Antidepressants

“Atypical” antidepressants

- Trazodone (1981)
- Bupropion (1985)
- Nefazodone (1994)
- Mirtazapine (1996)
- Vilazodone (2011)
- Vortioxetine (2013)


NORADRENERGIC
SEROTONERGIC
AXON
AXON
MAO inhibitors
Metabolites
MAO
MAO
Metabolites
Bupropion
NE
5-HT
α_2 (autoreceptor) adrenergic receptor
TCAs, SNRIs
Mirtazapine
TCAs, SSRIs, SNRIs, trazodone
NE reuptake
5-HT reuptake
NE receptor
5-HT receptor
POSTSYNAPTIC NEURON

Bupropoion

- NDRI (norepi-dopamine reuptake inhib.)
- Treats depression, ADHD, Nicotine Use D/o
- Potent 2D6 inhibitor
- Seizure risk is much lower (1/10,000) with XL form
- Other risks: anxiety, insomnia, palpitations, HTN
- Monotherapy and secondary agent
  - Most common way to “augment” SSRI/SNRI

Mirtazapine

- Tetracyclic “NaSSA”
  - Dual noradrenergic and specific serototinergic antidepressant
- Pharmacology:
  - Inhibits presynaptic α-2 adr. receptors, increasing serot. and norepi.
  - Blocks 5-HT 2 and 3, increasing NE and enhancing 5HT-1a-mediated serotonergic transmission
  - High affinity for H1 (why it works for insomnia best at low doses)
- ADR’s: Drowsiness, dry mouth, appetite/weight, *not* sexual ADR’s
- Clinical use: 7.5-15mg for sleep, 15-45mg for depression

Serotonin modulators

- *Trazodone*
  - SERT, 5HT-2a antag., also blocks H1 and α-1
  - 100-400mg/d split 2-3x/day is typical MDD dose
  - 3A4 substrate
  - ADR's: Sedation, weight gain; Qtc, priapism
- *Nefazodone*
  - SERT/NET, 5HT-2 and α-1
  - Hepatotoxic (1 case per ~250,000 pt-yrs)
  - 3A4 strong inhibitor & substrate

Vortioxetine and vilazodone

- *Vilazodone* (2011):
  - Reuptake inhibitor + 5HT 1a autorec. agonist (~buspirone)
  - Biggest issue is GI ADR's
- *Vortioxetine* (2013):
  - Reuptake inhibitor plus
    5HT-3, 1D, 7 antag., 1A agonis, 1B partial agonist
  - Claim: improved cognitive dysfunction

Choosing: VA MDD Guidelines (2022)

- **First choices:**
  Buproprion, mirtazapine, SSRI, SNRI, trazodone, (vilazodone, vortioxetine)
- **If no response, switch:**
  TCA/MAOI or ketamine, esketamine, nefazodone
- **If partial response, add:**
  Psychotherapy, atypical antipsychotic
- **If partial or no response to two or more trials:**
  Consider transcranial magnetic stimulation, ketamine/esketamine
- **Severe MDD w/ Catatonia, psychosis, severe SI, relevant history:**
  Consider ECT

Therapy in Depression

Treatment Guidelines

- **VA Guidelines** (2022):
  - If **uncomplicated** MDD, **patient preference** Rx vs therapy, and indiv. vs group Tx
  - If partial response to initial Rx, **add psychotherapy**
  - For moderate MDD when **breastfeeding or pregnant**, **psychotherapy** first line
  - **Combination** of Rx + Tx: **severe** (PHQ-9>20), **persistent** (2+ years), **recurrent** (2+ episodes)
- **American Psychological Association** recommends 7 therapies for MDD:
  - Behavioral, Cognitive, CBT, IPT, MBCT, Psychodynamic, Supportive
  - For older adults: **group CBT** or **Life Review/Reminiscence** therapy

Effective Psychotherapies for the Treatment of Major Depressive Disorder

The Military Health System and the Department of Veterans Affairs offer several effective, evidence-based treatments for treating Major Depressive Disorder (MDD). When treating uncomplicated MDD, the 2022 Department of Veterans Affairs/Department of Defense clinical practice guidelines (CPG) for MDD state, "We recommend that MDD be treated with either psychotherapy or pharmacotherapy as monotherapy, based on patient preference... when choosing psychotherapy to treat MDD, we suggest offering one of the following interventions (not rank ordered): Acceptance and commitment therapy, behavioral therapy/behavioral activation, cognitive behavioral therapy, interpersonal therapy, mindfulness-based cognitive therapy, problem-solving therapy, short-terms psychodynamic psychotherapy." (p. 33)[1]

Acceptance and Commitment Therapy (ACT): The ACT approach encourages acceptance of emotional distress and encourages the choice of goal-directed behaviors. A primary focus of ACT is to help the patient acknowledge difficulties in their life without feeling the need to escape from or avoid emotions.

Cognitive Behavioral Therapy (CBT): The CBT approach explores the connection between the thoughts and behaviors of patients. Many times, depression and its associated behaviors emerge from negative thoughts about oneself and their worth. Since both thoughts and behaviors are learned, patients can learn to establish new skills and patterns of thought that will help improve their mood.

Mindfulness-Based Cognitive Therapy (MBCT): Similar to a CBT approach, MBCT adds mindfulness-based skills such as meditation, imagery and experiential exercises to help patients overcome negative thoughts. MBCT teaches patients to pay attention to their thoughts and feelings without judging them.

(NEW!) Short-Term Psychodynamic Psychotherapy (STPP): This is the only new psychotherapy approach added to the 2022 MDD CPG. The STPP approach includes helping patients gain a self-understanding of the negative relationship patterns they are repeating. It also focuses upon current relationship conflicts and setting interpersonal goals.

Behavioral Therapy/Behavioral Activation (BT/BA): The BT/BA approach emphasizes the use of daily enjoyable activities and life events to help decrease depression. When patients become depressed, they can discontinue their routine and withdraw from their environment. Over time, this withdrawal can make depression worse. BT/BA encourages patients to engage in pleasurable activities that have been shown to improve mood.

Interpersonal Therapy (IPT): The IPT approach helps patients solve relationship problems. This may include problems with family members, friends and co-workers. The approach has been demonstrated to be effective in improving communication, conflict resolution, distress tolerance and increasing problem-solving skills.

Problem-Solving Therapy (PST): The PST approach focuses upon solving problems, achieving goals and changing behaviors. By defining the current problems experienced by the patient and developing a step-by-step method for solving them, the patient's overall mood improves.

Selecting an antidepressant

- Past **personal response** (+/- family response)
- **Side effect profile** (GI, sexual ADR's, sedation, weight gain, etc)
- Drug **interactions**
- Patient **preference**
- **Concurrent psychiatric or medical d/o**
  - Pain—SNRI or paroxetine (though NNT ~6-7 for 20% reduction)
  - CV disease, CKD – sertraline best studied, but not only option
  - Pregnancy—avoid paroxetine, venlafax; others risk-risk decision
  - Breastfeeding—sertraline best studied, but not only option (Lactmed)
- **Cost**
- **NOT**: FDA Indication, Ads, Reps!

AGENDA

Focus on Therapeutic Alliance

Master starting and stopping antidepressants

Identify and treat comobidities

Review the “atypical antidepressants” (bupropion, mirtaz., etc.)

Demystify augmentation: light, exercise, supplements, thyroid, atypicals

Introduce newer treatments (ketamine, neurosteroids, TMS, psilocybin)

Augmentation

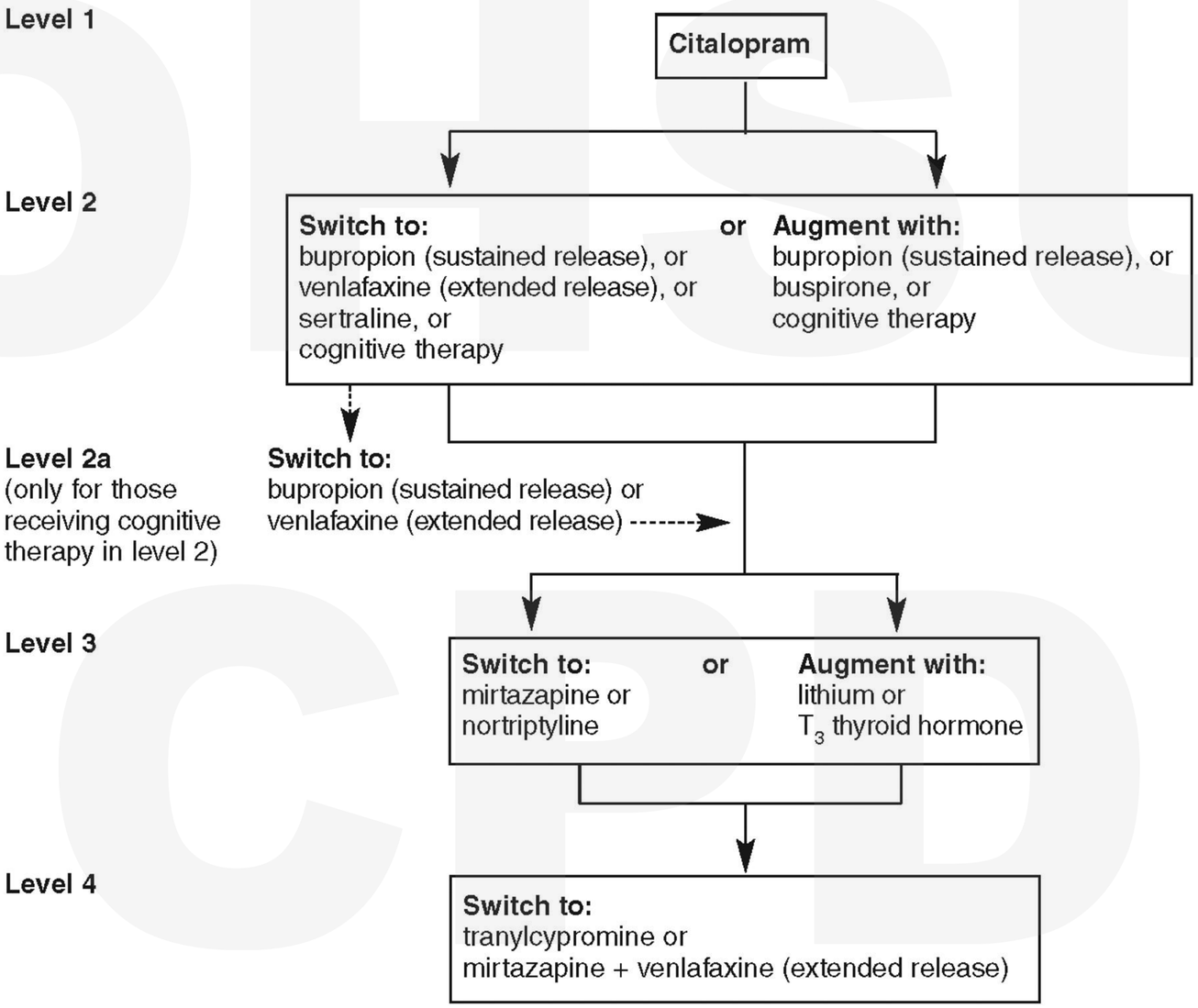
Depression Treatment

The STAR*D Trial (2000-04)

- Largest trial of depression ever conducted (41 centers, 4,041 patients)
- Publicly funded by NIMH
- 5 visits over 12 weeks w/ HAM-D and QIDS-SR guiding decisions including dose
- Exclusion: psychotic depression, bipolar, primary Dx of OCD or EDO, Sz
- Practical (not controlled) trial
- Aimed to establish best “next steps” for adults with MDD
- Extensively published (100’s of papers) and debated results

Figure 1

STAR*D treatment levels



Gaynes, et al. 2009

Depression Treatment

The STAR*D Trial (2000-04) — Results

- Level 1: 2,876 completed
  - Remission = 27-33%, response = 47%, 47 days
  - Remission ~ Caucasian race, female, employment, higher education/income
  - Lower rates ~ chronicity, comorbidity (SUD, anxiety d/o's), medical comorbidity, lower functioning or quality of life at baseline
  - 40% of remitters required 8+ weeks to do so
- Level 2: 727 randomly switched to sertraline, venlafaxine, bupropion
  - Remission rates were similar (21-27%)
- Level 2: 565 randomly assigned to augmentation with bupropion, buspirone, or therapy
  - Remission rates were similar (~30%), tolerability: therapy > bupropion > buspirone

Gaynes, et al. 2009

Depression Treatment

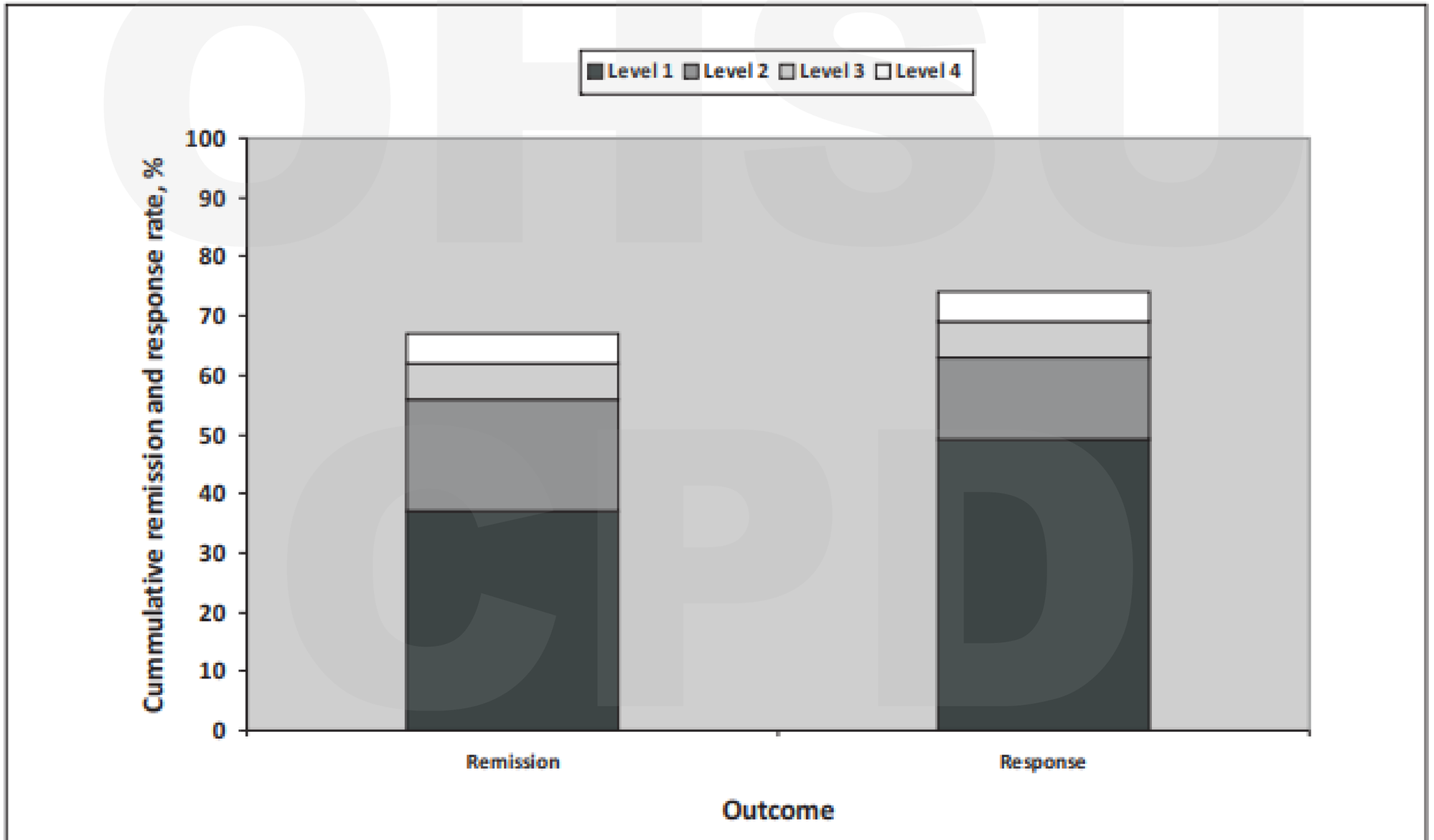
The STAR*D Trial (2000-04) — Results, cont.

- Level 3: 235 switched to mirtazapine (remission = 8-12%) or nortriptyline (12-20%)
- Level 3: 142 added lithium (13-16%) or T3 (25%, better tolerated)
- Level 4: 109 who failed 3 aggressive trials. “Treatment resistant”
  - Switched to switched to mirtaz + venlafax (14-16%) vs tranylcypromine (7-14%)
- Limitations are many:
  - No control group taking a placebo
  - Patient preferences were included in decisions
  - Not set up to analyze switch vs augmentation strategies
  - Very few patients selected cognitive therapy (cost, availability?)

Gaynes, et al. 2009

STAR*D

Figure 3 Cumulative remission and response rates across all 4 treatment levels



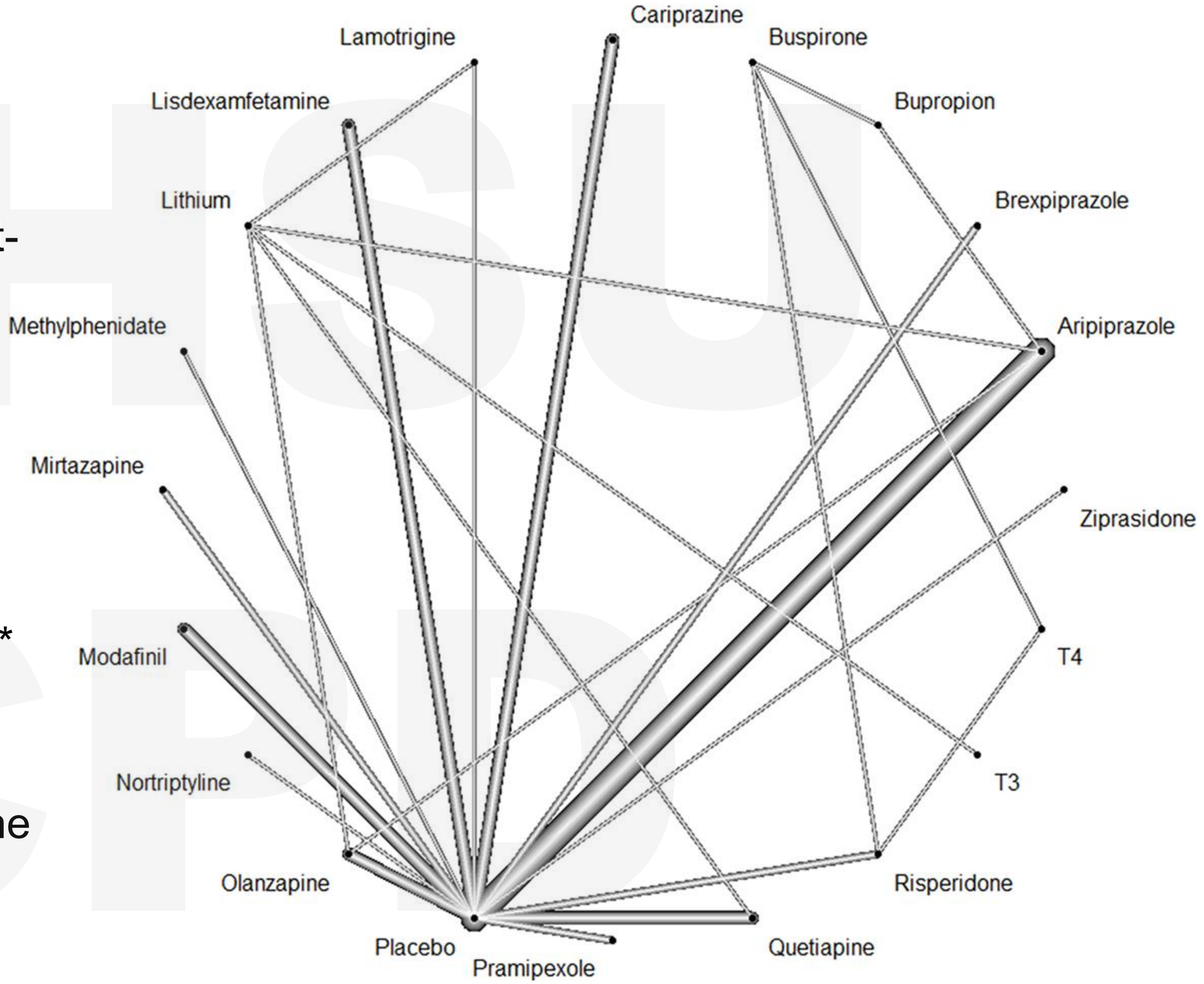
Augmentation

Nunez, et al J Affective Disorders 2022

- Network meta-analysis in treatment-resistant depression
- N=65 studies
  12,415 patients
- <u>Remission rates > placebo</u>:

  T4, aripiprazole, brexpiprazole, risperidone, quetiapine, olanzapine*
- <u>Discontinuation > placebo</u>:

  ziprasidone, mirtazapine, cariprazine



Choosing: VA MDD Guidelines (2022)

- **First choices:**
  Buproprion, mirtazapine, SSRI, SNRI, trazodone, (vilazodone, vortioxetine)
- **If no response, switch:**
  TCA/MAOI or ketamine, esketamine, nefazodone
- **If partial response, add:**
  Psychotherapy, atypical antipsychotic
- **If partial or no response to two or more trials:**
  Consider transcranial magnetic stimulation, ketamine/esketamine
- **Severe MDD w/ Catatonia, psychosis, severe SI, relevant history:**
  Consider ECT

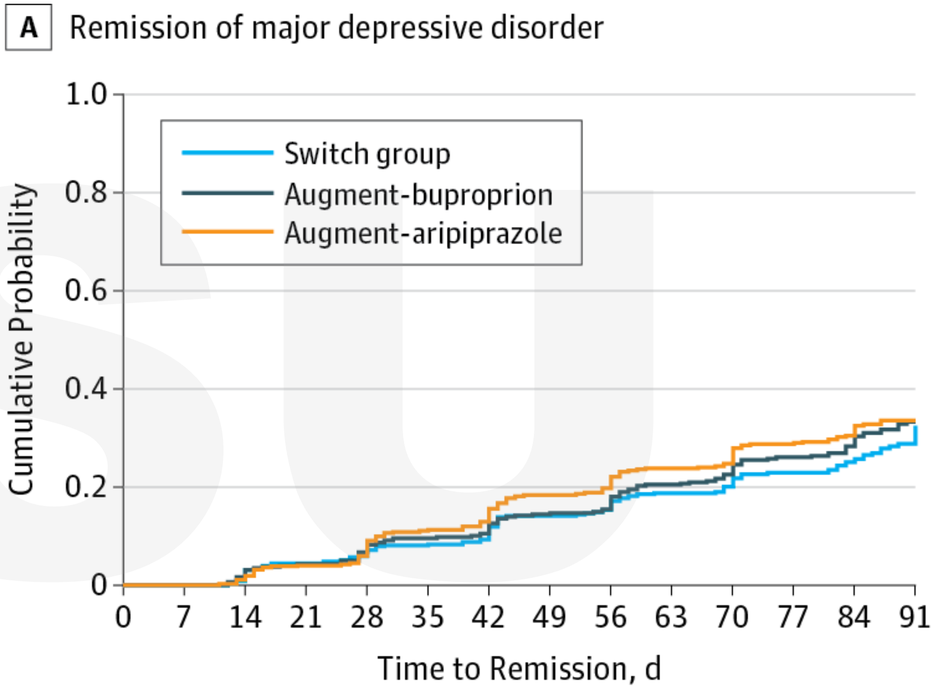
VAST-D

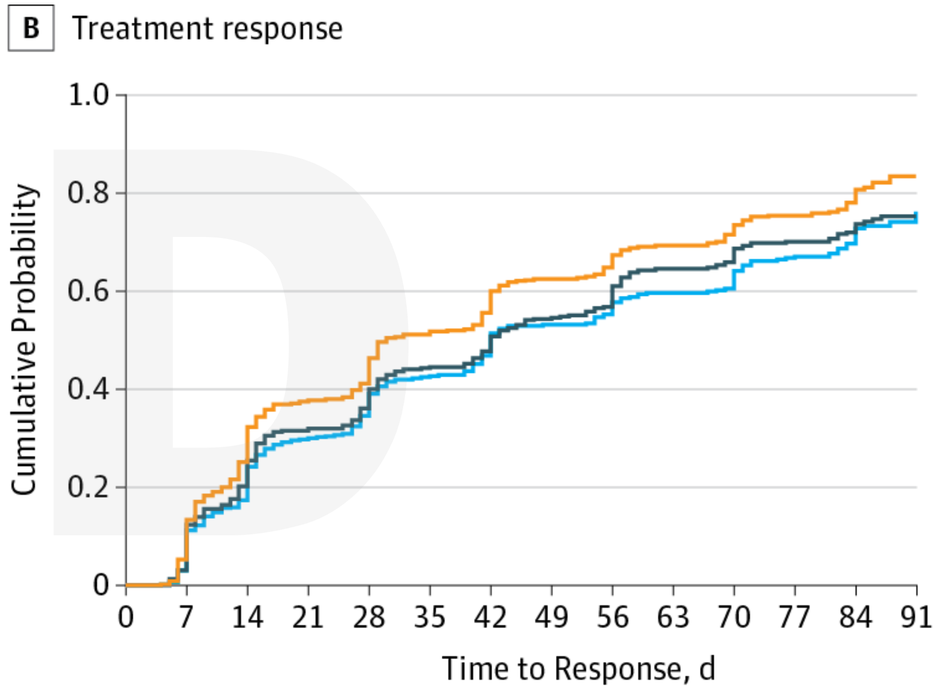
Switch vs Augmentation

N = 1522 antidepressant nonresponders, randomized to:

1. Switch to bupropion
2. Augment with bupropion
3. Augment with aripiprazole

ADR's (Fatigue, increased appetite/weight, akathisia, abnormal labs, wt gain of 7% of greater) more common in agument-aripiprazole group





Aripiprazole

Dose & ADR's

- Start low (1-2.5mg) and stay in 1-5mg range for most
- If potent **2D6 inhibitors** (fluox, parox) start at 1/2 that dose & monitor closely
- **Common ADR's**:
  akathisia (25%), restlessness (12%), insomnia (8%), fatigue (8%), blurred vision (6%), constipation (5%), dizziness (4%), sedation, (4%), and weight gain (3%
- Serious: Impulse control disorders, OCD
- For **akathisia**, reduce dose or add mirtazapine, trazodone, propranolol or benzodiazepine
- **For appetite/weight**, add metformin (or GLP-1?)

BJPsych The British Journal of Psychiatry (2022)
221, 440–447. doi: 10.1192/bjp.2021.165

Review

Optimal dose of aripiprazole for augmentation therapy of antidepressant-refractory depression: preliminary findings based on a systematic review and dose–effect meta-analysis

Yuki Furukawa, Tasnim Hamza, Andrea Cipriani, Toshi A. Furukawa, Georgia Salanti and Edoardo G. Ostinelli

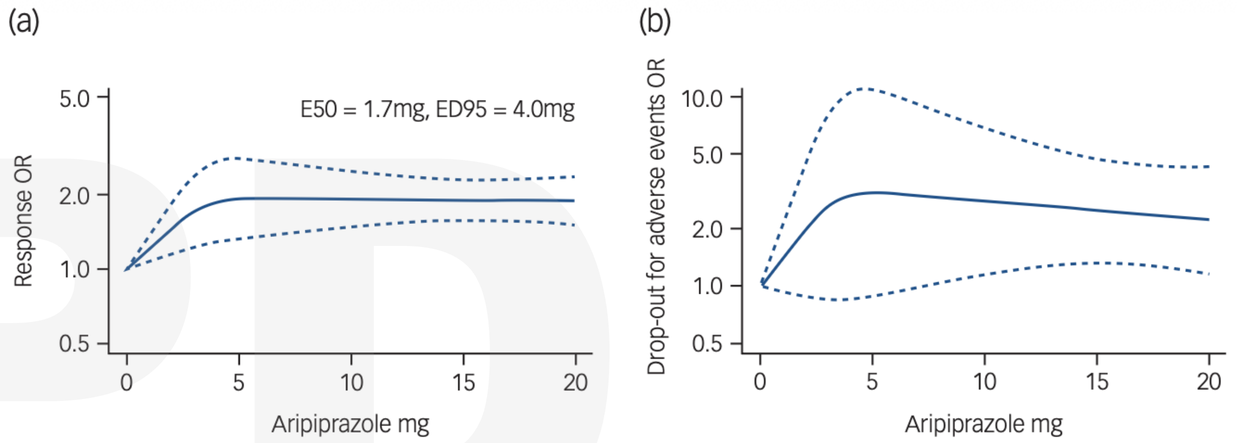


Fig. 2 Dose–effect relationships for aripiprazole augmentation in antidepressant-refractory de adverse events. (c) Drop-out for any reason. ED50, 50% effective dose; ED95 95% effective dos intervals.

Thyroid hormone

Cytomel (T3)

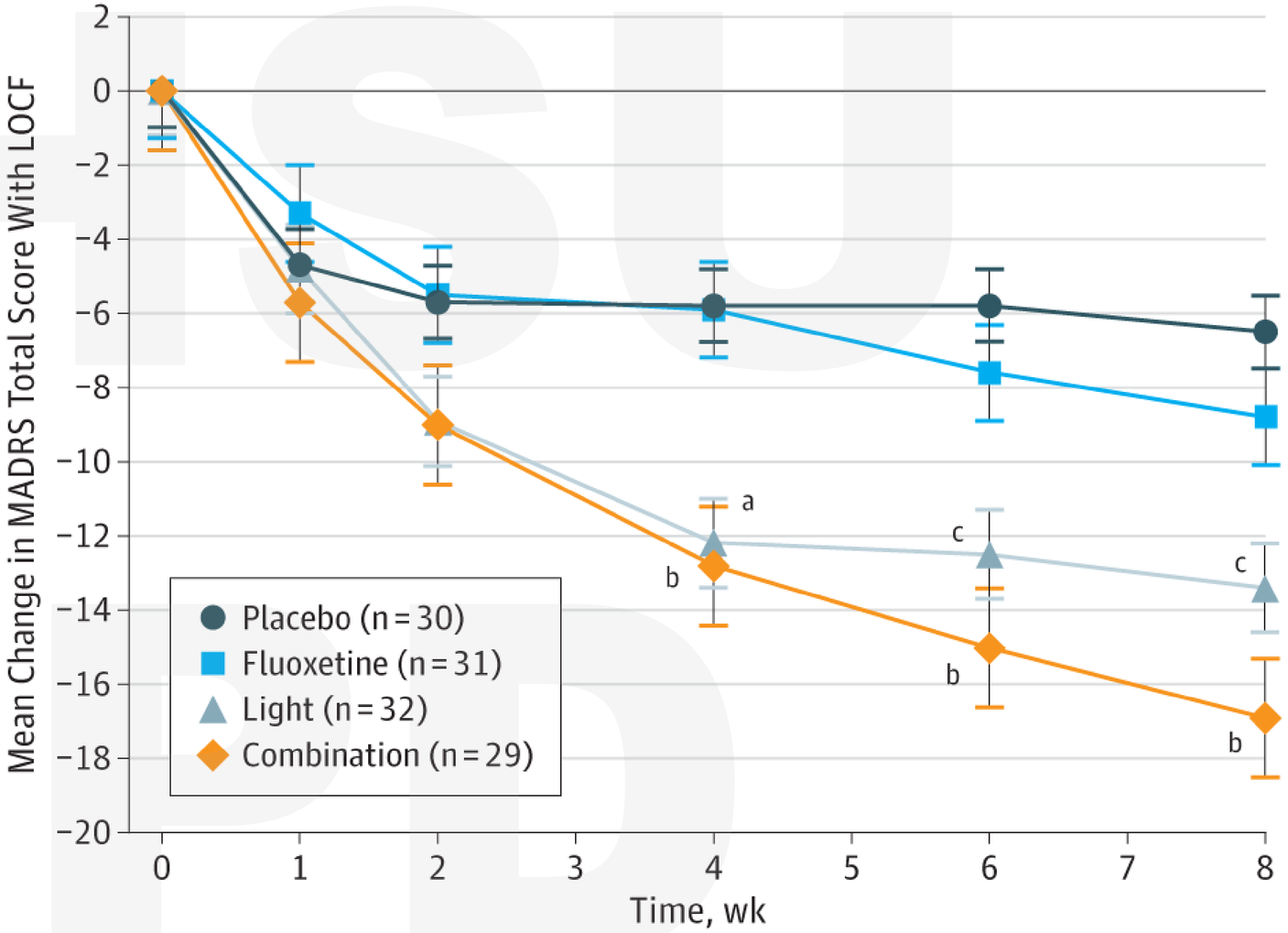
- In the **euthyroid** patient
- Preferred > T4
- VA Guidelines (2022):
  Start at 25mcg daily, advance to **target 50mcg**, 62.5mcg max
- For older adults, can start much lower (e.g. 5mcg and increase slowly as tolerated)
- Recent metaanalyses w/ high-quality RCT data cast doubt

Non-Rx options

Evidence-Based

- **Light device**
- **Psychotherapy** (All of them!)
- **Exercise**
- **Brain stimulation** (TMS)
- Some **neutraceuticals** (Sam-e, creatine, lavender?)

RCT of light vs fluox vs both in nonseasonal



Antidepressant “Augmentation”

- Common strategy for *partial responders*
- Options include:
  - + **psychotherapy** and other psychosocial interventions
  - + complementary antidepressants:
    - **Bupropion** for patients with fatigue, lower energy
    - **Mirtazapine** for insomnia, low appetite, IBS Sx
    - **Trazodone** for insomnia
    - **TCA** for sleep, pain, headache, or higher doses for mood
- + atypical **antipsychotics:** e.g. **aripiprazole** (see VAST-D), **quetiapine**, etc.
- + others: **Lithium**, **thyroid hormone (T3/T4)**, **psychostimulants**
- + **neutraceuticals:** Sam-e, methylfolate, etc

AGENDA

Focus on Therapeutic Alliance

Master starting and stopping antidepressants

Identify and treat comobidities

Review the “atypical antidepressants” (bupropion, mirtaz., etc.)

Demystify augmentation: light, exercise, supplements, thyroid, atypicals

Introduce newer treatments (ketamine, neurosteroids, TMS, psilocybin)

AGENDA

Focus on Therapeutic Alliance

Master starting and stopping antidepressants

Identify and treat comobidities

Review the “atypical antidepressants” (bupropion, mirtaz., etc.)

Demystify augmentation: light, exercise, supplements, thyroid, atypicals

Introduce newer treatments (ketamine, neurosteroids, TMS, psilocybin)

Newer treatments in psychiatry

(Ketamine, psilocybin, etc.)

Ketamine

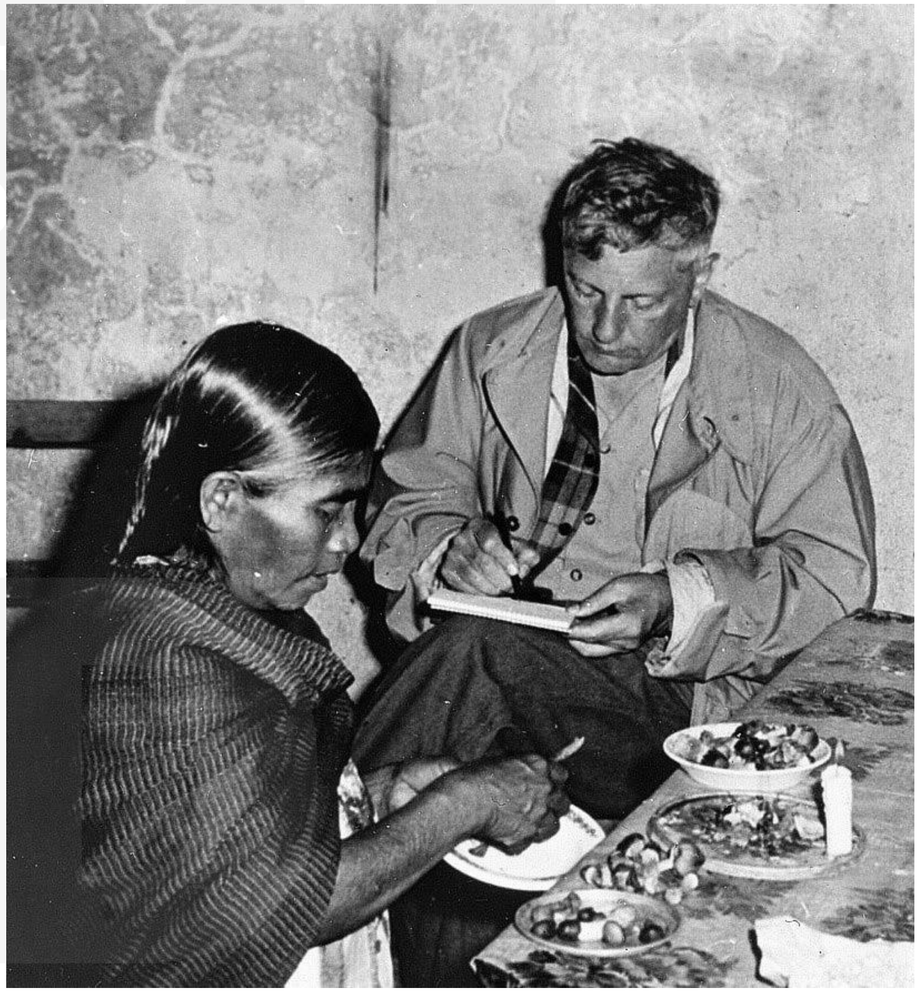
- NMDA receptor antagonist
  - Also evidence of opioid receptor, AMPA activity
- Dissociative anesthetic common in ED, OR, pain clinics
- **Rapid-acting antidepressant** in subanesthetic doses
  - IV: 0.5mg/kg, sometimes up to 1.0
- Multiple forms:
  - Racemic mixture is available IV, IM, PO
  - S- enantiomer (esketamine) intranasal is FDA approved for depression
  - R- (Arketamine) is being investigated
- Used in several ways in psychiatry, including to **assist psychotherapy**

GABA neurosteroids

- Positive allosteric modulation of GABA-A receptor
- Rapid acting antidepressants
- First FDA approval for Post-partum depression
- Two available:
  - Brexanolone (approved 2019, withdrawn 2024)
    - Continuous IV infusion requiring monitoring over 60 hours
    - ADR's: sedation/somnolence/LOC, dry mouth, flushing
  - Zuranolone (2023)
    - 50 mg once daily for 14 days
    - ADR's: somnolence, dizziness, diarrhea, fatigue

Psilocybin

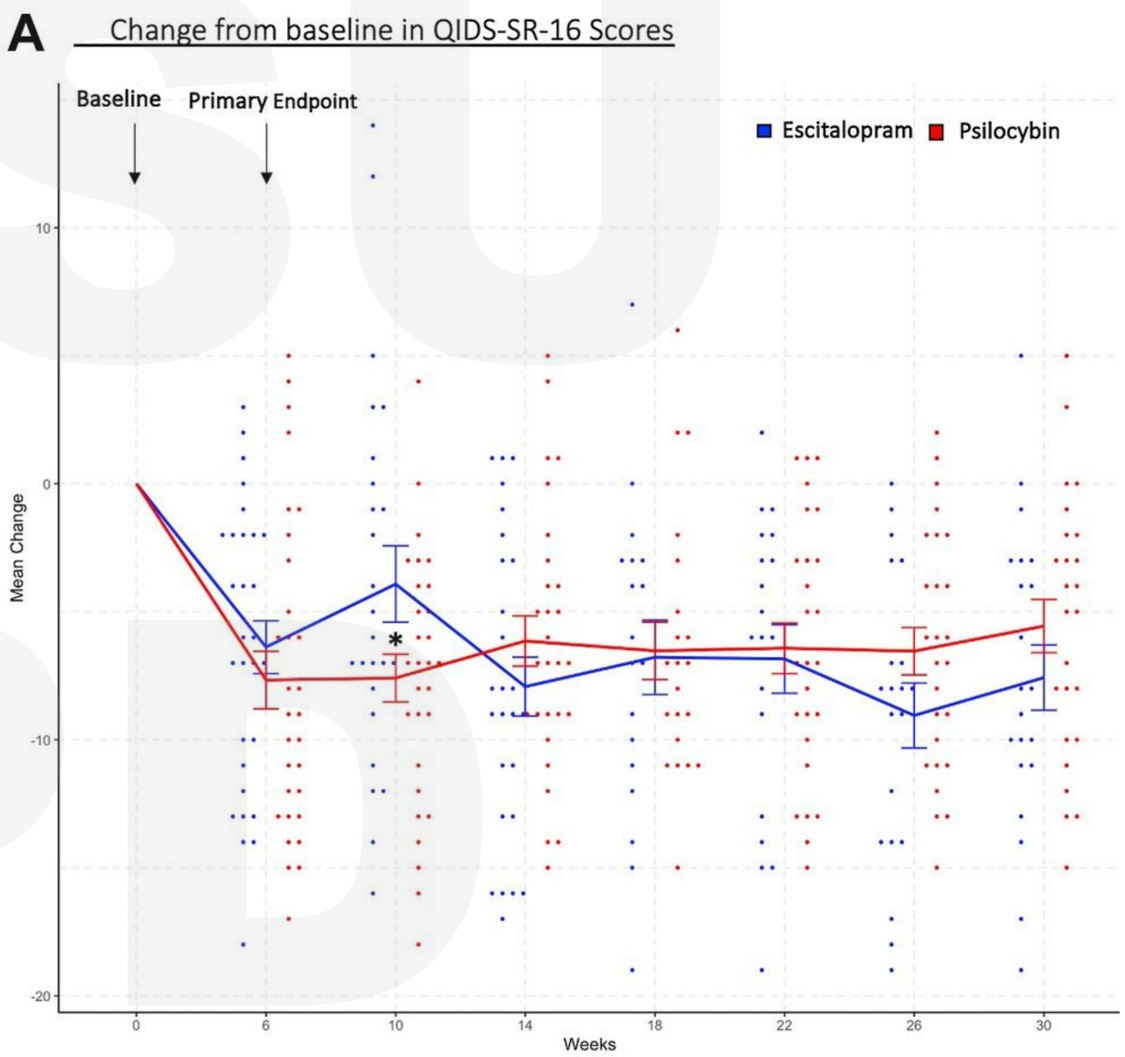
- A classic “psychedelic” w/ 5HT-2a agonism
- Discovered/stolen by Gordon Wasson from the Mazatec in Oaxaca, popularized in *Life (1957)*
- *Requires ~8 hour dosing session w/ therapist present, +/- preparation/integration therapy*
- Induces *nonordinary/mystical* states of consciousness
- Legal status is in flux:
  - DEA schedule 1 agent (“no therapeutic use”)
  - Non-medical pathway in Oregon



Maria Sabina and Gordon Wasson

Psilocybin, cont

- Multiple trials showing efficacy, safety as an antidepressant
- Interactions:
  - Lithium can produce seizures
  - Serotinergic antidepressants can block the experience
- Currently in Phase III, e.g. by Usona Institute
- *FDA approval in 2027-28?*



Erritzoe, et al 2024 in press

AGENDA

Focus on Therapeutic Alliance

Master starting and stopping antidepressants

Identify and treat comobidities

Review the “atypical antidepressants” (bupropion, mirtaz., etc.)

Demystify augmentation: light, exercise, supplements, thyroid, atypicals

Introduce newer treatments (ketamine, neurosteroids, TMS, psilocybin)

Thank you and GOOD LUCK!

Ryan.Blum@va.gov (until May)
ryan@ryanblummd.com