The Much Too Medicated Patient

Chris Aiken, MD
Editor-in-Chief, *Carlat Report*

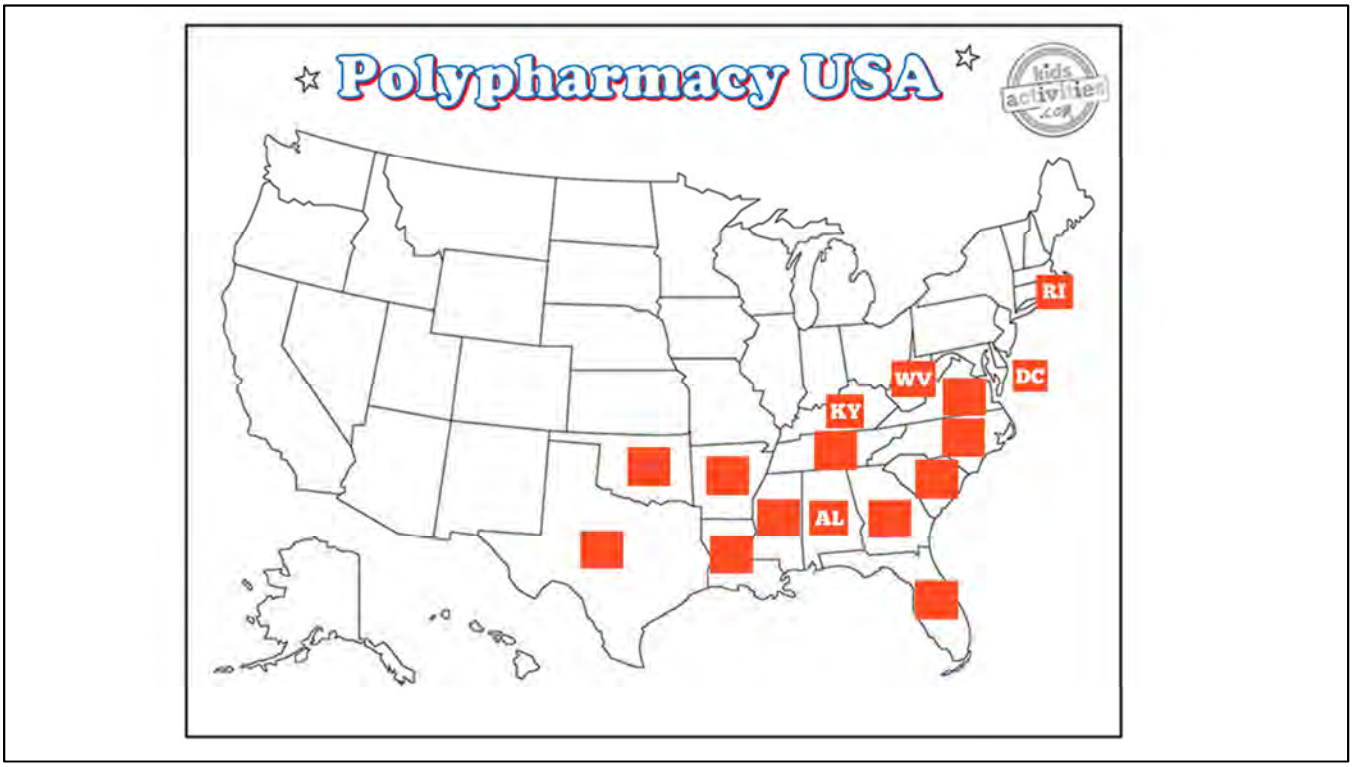
Assistant Prof Psychiatry,
NYU and WFU Medical Schools





Disclosure

In compliance with the ACCME Standards for Commercial Support of CME, as the speaker I do not have any relevant financial relationships to disclose in relation to this presentation.

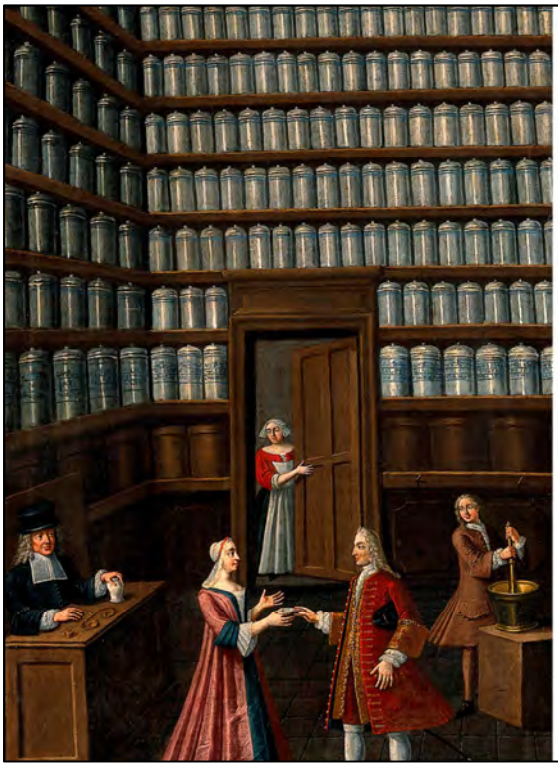


Rates of polypharmacy 1.5 times higher in southeast; WV highest (particularly southern part), also high = AL, KY, DC, RI. More common in women, developmental disabilities, and Medicaid populations

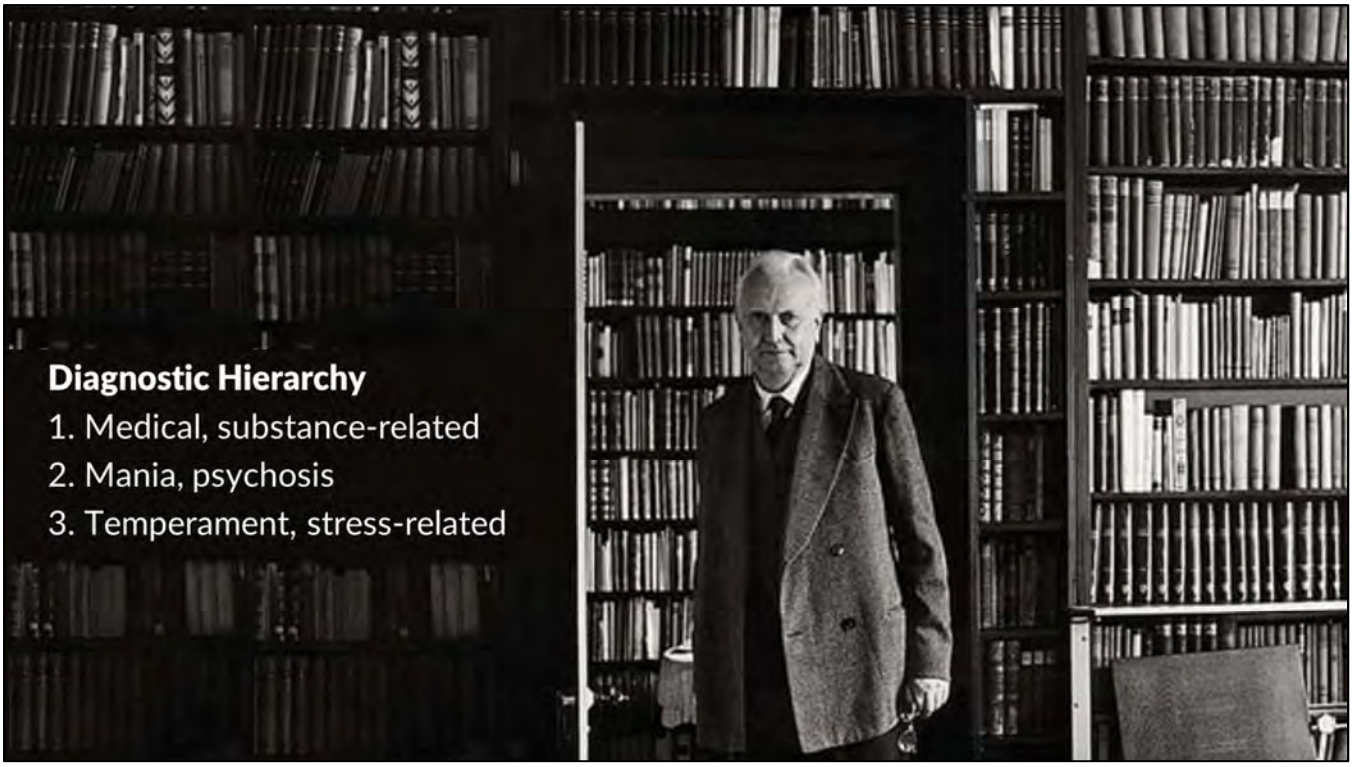
Supplements are not polypharmacy if natural to the body or common in the diet



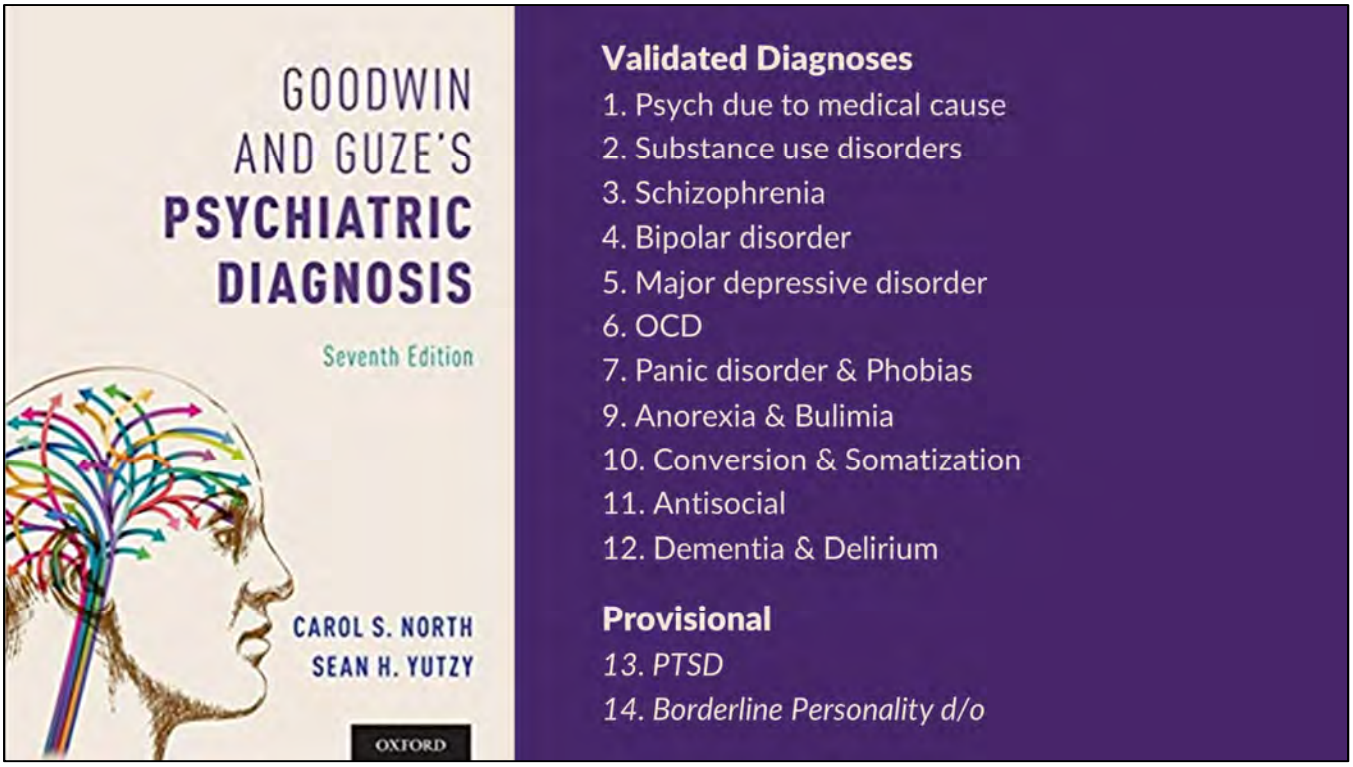
Phytochemicals are herbs and should be treated like medications. Nutraceuticals are safer and often have health benefits (they are already in the body), like vitamins, minerals, omega 3, probiotics.



Polypharmacy Prevention

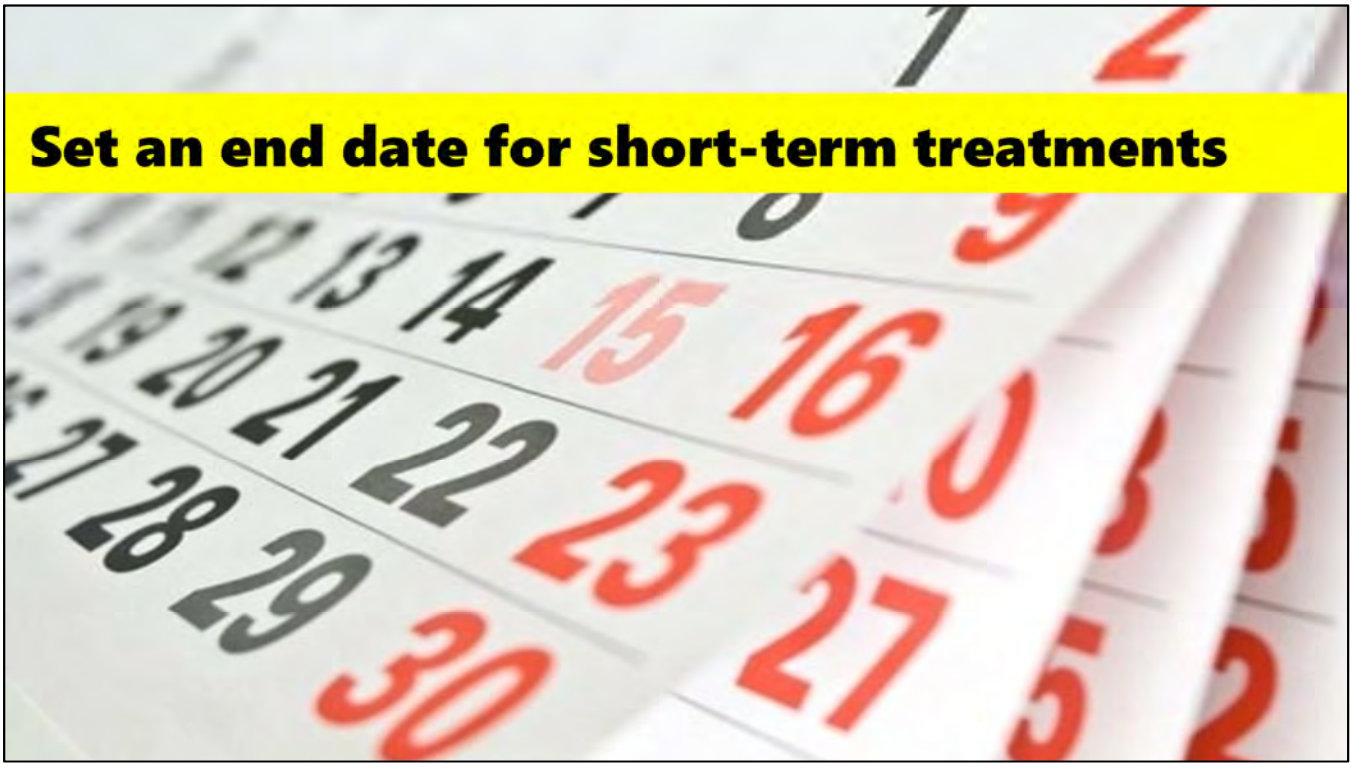


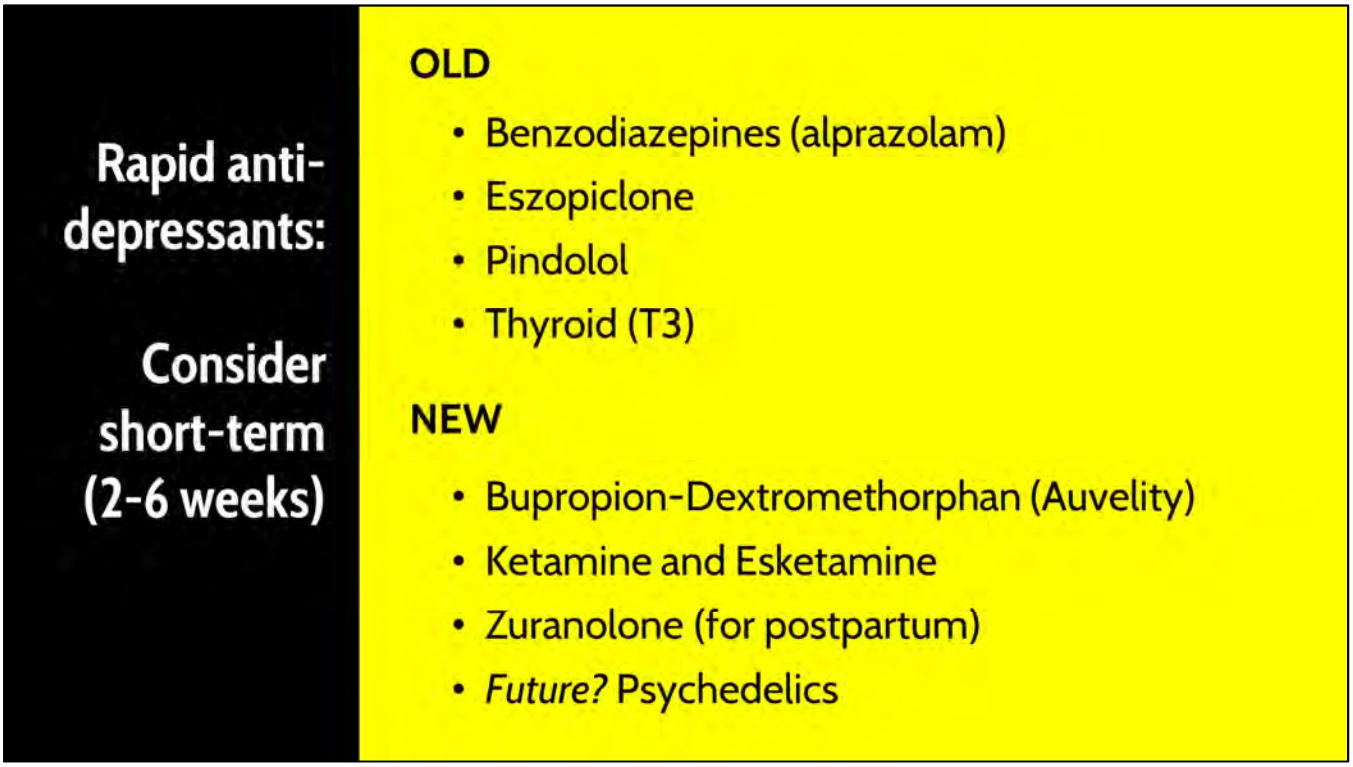
Karl Jaspers developed the diagnostic hierarchy behind the “do not diagnose if better explained by” clause in DSM



Sources for structured diagnostic testing:

-
-
-
-


Set an end date for short-term treatments



Eszopicline but not other z hypnotics accelerates antidep in GAD and MDD. Pindolol only works for accelerating SSRIs short term, and not other antidepressants (does not work for augmentation after SSRI is started). T3 well studied for antidep acceleration. Alprazolam has over a dozen trials for acceleration of antidepressants (core symptoms of depression) or to treat acute depression but is short-term.

Short-term Antipsychotic Augmentation

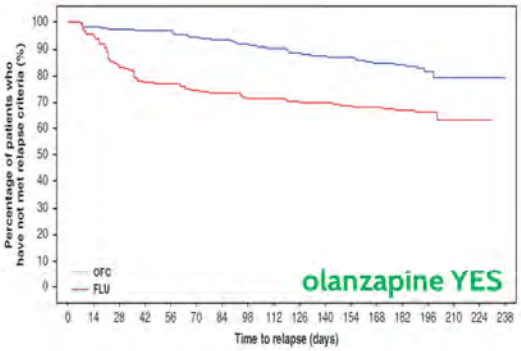
Taper after at least 6 months of remission in mood disorders

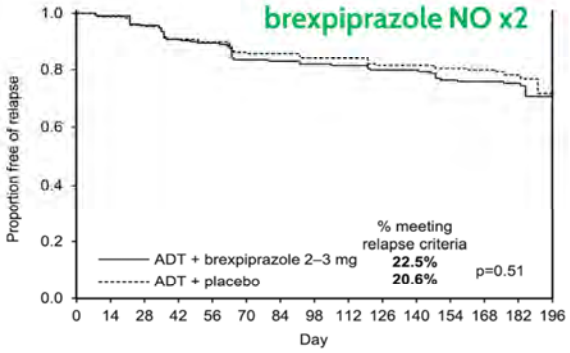


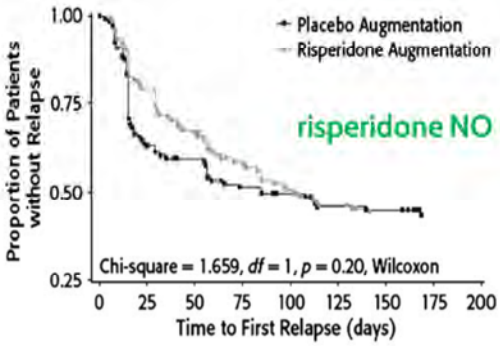
There is scant research on this 6 mth duration but is extrapolated from studies of antidepressants, one RCT successfully tapered of antipsychotic augmentation after 6 mth of recovery in bipolar mania (non-industry funded; whereas industry funded trials “proved” long-term efficacy by attempting to switch to placebo after 2-3 mth of recovery)

Do antipsychotics prevent unipolar depression?

Not in 3/4 trials (6 months, n=2,308)







These are all placebo controlled maintenance trials of antipsychotics in MDD – only positive for olanzapine which may be a withdrawal artifact in study. Quetiapine and aripiprazole have preventative data in controlled trials but they did not have a placebo control. Besides their long-term risks of TD and metabolic syndrome, antipsychotics are linked to higher cardiovascular comorbidity in depression (Tsai DH et al, Brit J Psychiatry 2025;1-9).

Psychotic Depression

May require long-term antipsychotic augmentation

Relapse
20% vs 55%

Flint AJ et al, JAMA 2019;322(7):622-31





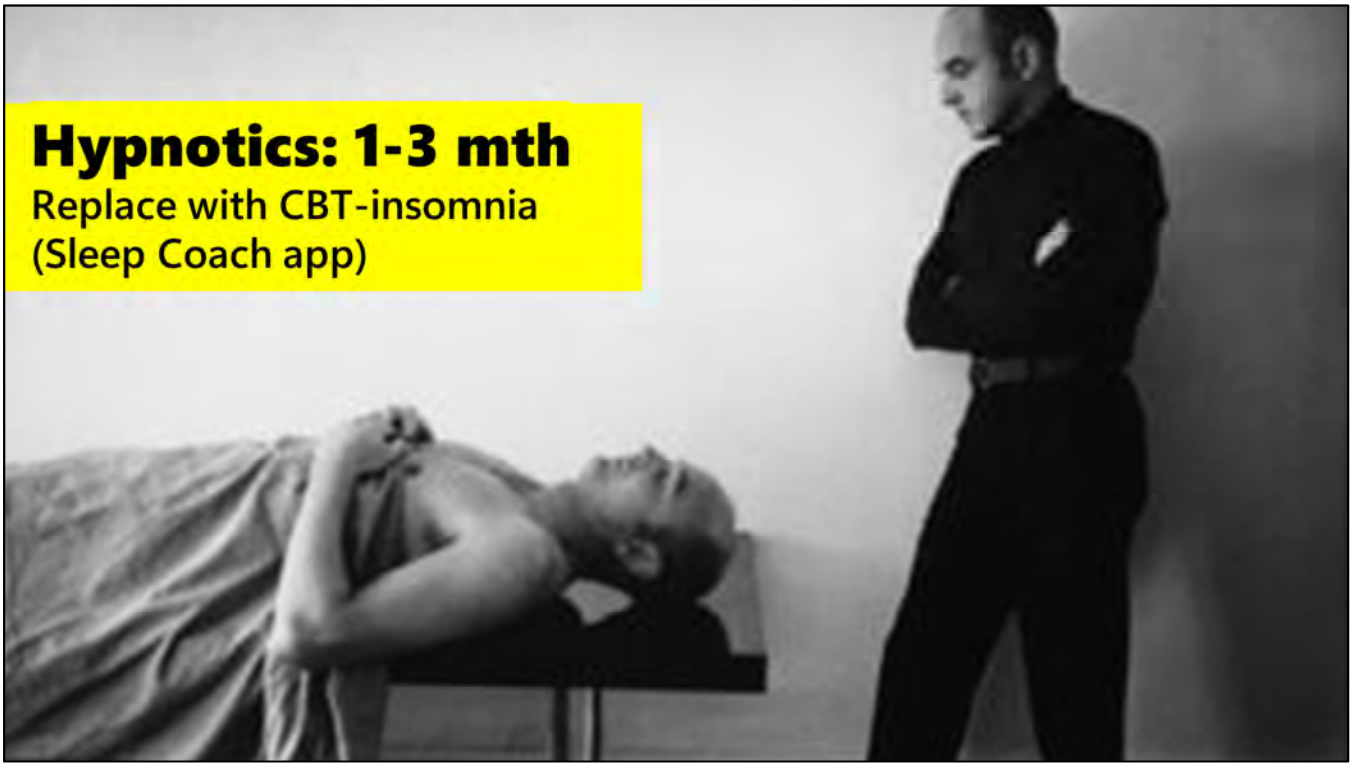
Time-limited stimulants

- Subthreshold ADHD
- ADHD that resolves in adulthood

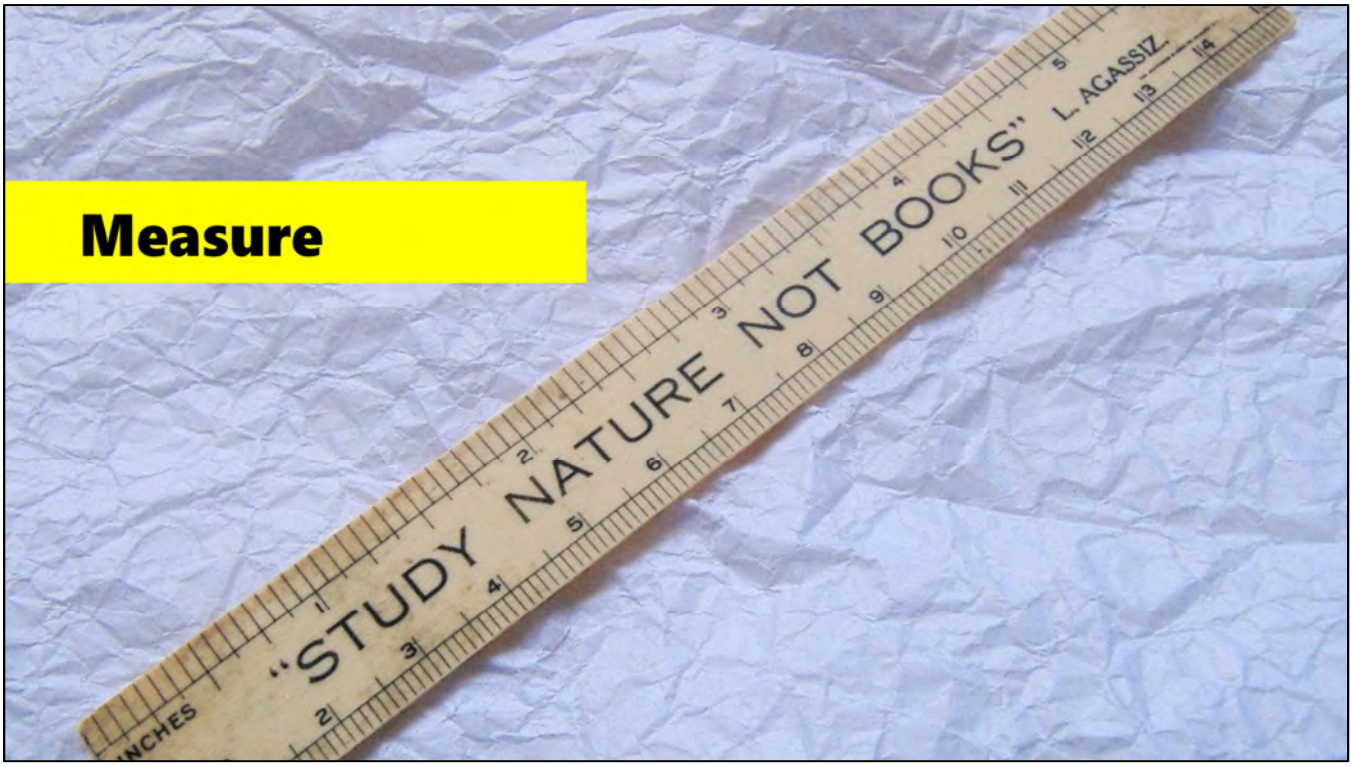


Short-term Anxiolytics

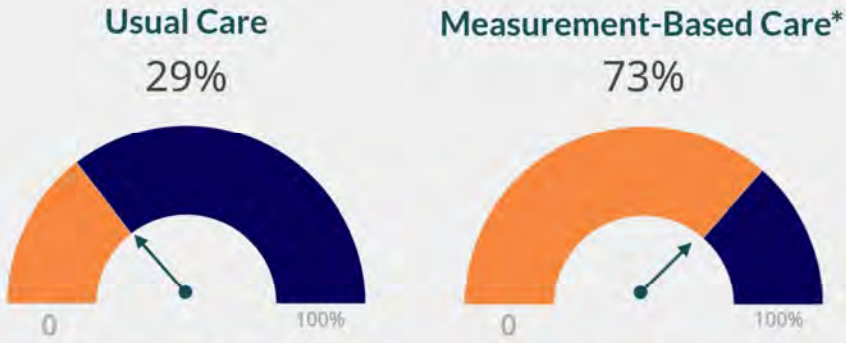
2-6 weeks ideal for benzodiazepines in acute anxiety



In most studies, researchers were able to switch hypnotics to placebo without loss of efficacy after acute phase of treatment


Measure
"STUDY NATURE NOT BOOKS"
L. AGASSIZ

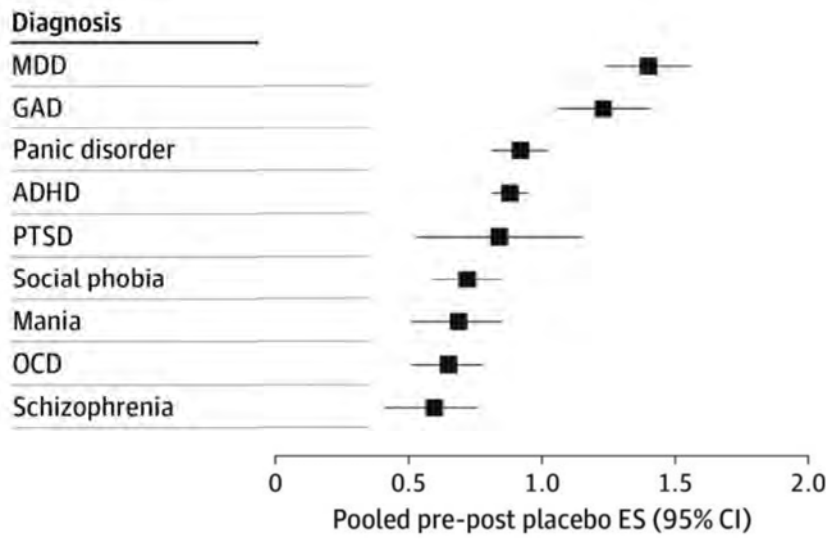
Regular Measurement Raises Remission in Depression



Guo T et al, *Am J Psych*, 2015;172:1004-13

*Self-rated QIDS with algorithm-guided care based on QIDS level. Both groups only allowed paroxetine and mirtazapine (n=120).

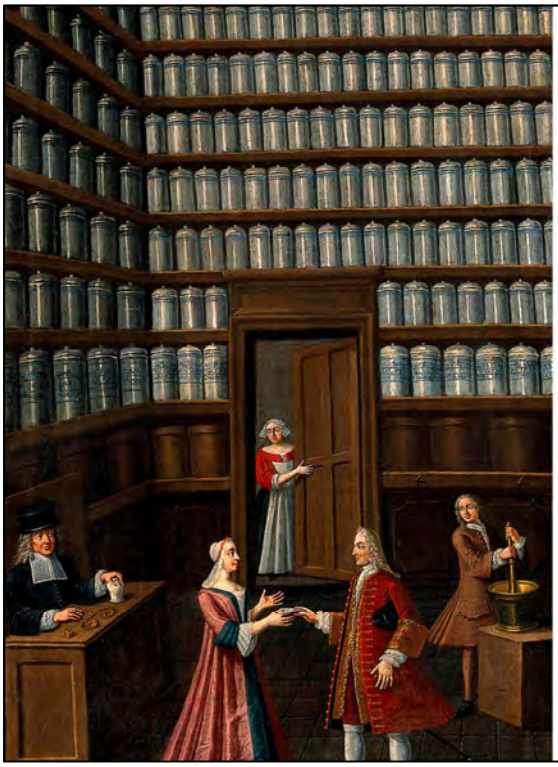
Placebo response by diagnosis



Bschor T et al, JAMA Psychiatry 2024;81(8):757-768.

Huneke NTM et al, Mol Psychiatry 2024;29(12):3915-3925.

Other predictors of placebo response = Children, female, milder symptoms, shorter duration of symptoms, alcohol use disorder. This makes it difficult ot figure out which meds are effective, but placebo response is not an “either or” phenomena where patients are either real responders or placebo responder. Rather, the placebo effect is imbedded in most response.



Polypharmacy Reduction

Before tapering

1. Secure alliance
2. Explain rationale
3. Understand hopes and fears
4. Get collateral input on response
5. If effective, wait for at least 6 months of full remission
6. Wait for stress to stabilize
7. Add behavioral change

Goldberg JF et al, JAMA Netw Open 2026;9(2):e260043

What to taper

1. Dangerous medications
2. Irrational combinations
3. High doses
   Exceptions in depression: Tricyclics, MAOIs
   Exceptions in schizophrenia: Olanzapine
4. Lacking evidence from controlled-trials or patients-history

Whether a medication is “dangerous” depends on patient factors. Irrational combinations are those that duplicate mechanisms (eg, guanfacine + clonidine), or mechanisms that counteract (eg, anticholinergic + cholinesterase inhib; stimulant + antipsychotic). 20 meta-analyses find no benefit with high dose antidepressants in depression, beyond equivalent of fluoxetine 20-30 mg, except for tricyclics, desvenlafaxine, and possibly MAOIs.

Optimal Antidepressant Doses

TABLE 15-1. Optimal Dose Ranges for Second-Generation Antidepressants

Antidepressant	Optimal Dose (mg/d)*	FDA Max in Depression
Citalopram	20–40	60
Escitalopram	10–20	20
Fluoxetine	20–40	80
Fluvoxamine	100–150	n/a
Paroxetine	20–30	50
Sertraline	50–100	200
Duloxetine	40–60	120
Desvenlafaxine	50–200	400
Venlafaxine	75–150	225
Bupropion	150–300	450
Mirtazapine	15–30	45
Nefazodone*	300–600	600
Trazodone*	150–300	600
Vilazodone	10–20	20
Vortioxetine	20–40	40

*Optimal doses are derived from dose-response curves from fixed-dose studies; that data is not available for nefazodone and trazodone (Furukawa TA et al, 2019; Hamza T et al, 2024)

Aiken C, *Difficult to Treat Depression,* 2025

Antipsychotic Max in Schizophrenia

Antipsychotic	95% effective dose	Response Plateau?
Aripiprazole	11.5 mg	Yes
Asenapine	15 mg	Yes
Brexpiprazole	3.4 mg	Yes
Haloperidol	6.3 mg	Yes
Iloperidone	20.1 mg	Possibly not
Lurasidone	147 mg	Possibly not
Olanzapine	15.2 mg	**NO (efficacy in refractory cases at 25-50 mg/day)**
Paliperidone	13.4 mg	Possibly not
Quetiapine	482 mg	Yes
Risperidone	6.3 mg	Yes
Ziprasidone	186 mg	Yes

Leucht S et al, Am J Psychiatry. 2020;177(4):342-353.

Olanzapine is the only antipsychotic with evidence for greater efficacy at higher doses (25-50 mg)

High dose stimulants in ADHD

Benefits pleatuea and risks worsen above....

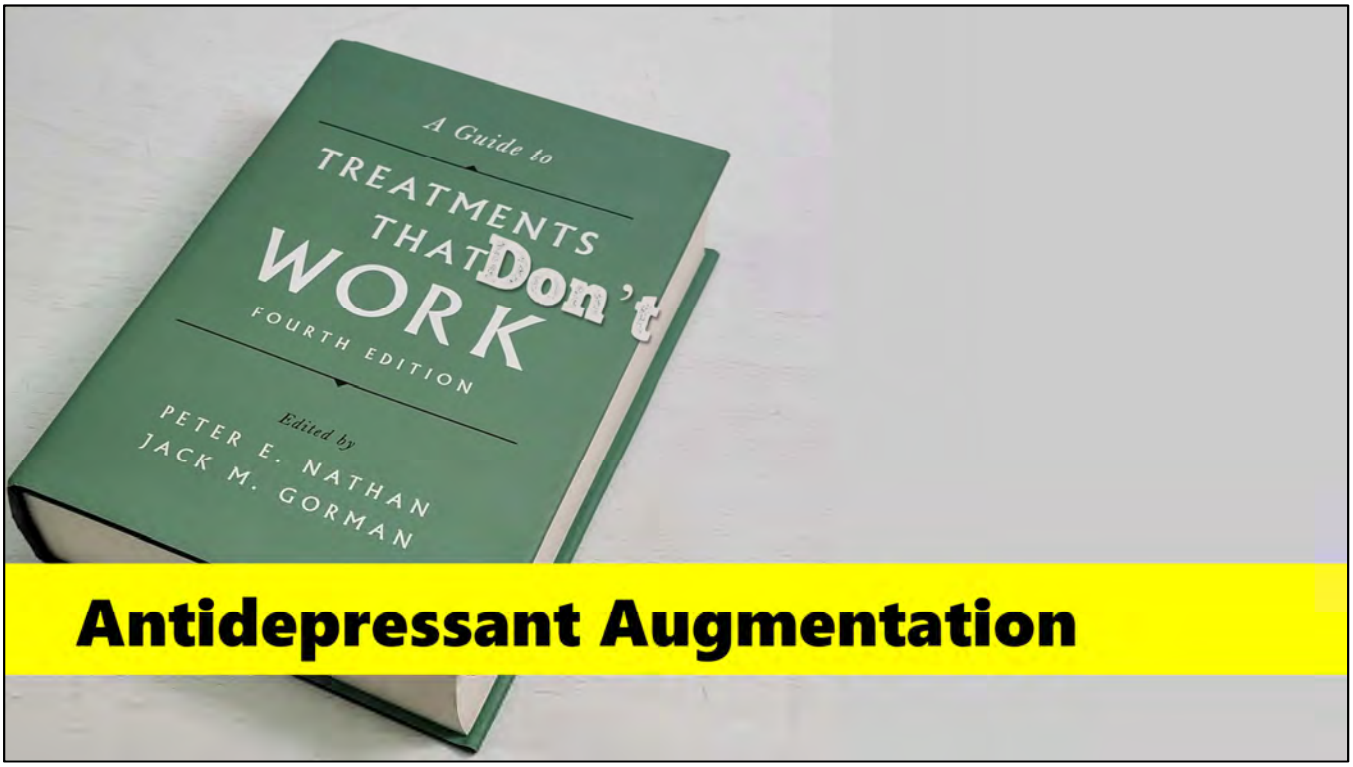
Amphetamines

- Mixed amphetamines (Adderall) 35 mg
- Dextroamphetamine 30 mg
- Lisdexamfetamine (Vyvanse) 80 mg

Methylphenidates

- Methylphenidate 60 mg
- Dexmethylphenidate 30 mg

Farhat LC, et al. JAMA Psychiatry. 2024;81(2):157-166


A Guide to
TREATMENTS THAT Don't WORK
FOURTH EDITION
Edited by
PETER E. NATHAN
JACK M. GORMAN
Antidepressant Augmentation

1	3	2
Bupropion	**Mirtazapine**	**Buspirone**
5	8 small	
Stimulants	**Lamotrigine**	

These strategies gained popularity through small or uncontrolled trials, only to fail in large trials.

Above each medication are the large randomized controlled trials where it failed as antidepressant augmentation. In most cases, these are large randomized trials and there are no positive large trials (lamotrigine is an exception where all are small trials, and failed in meta-analysis of them).

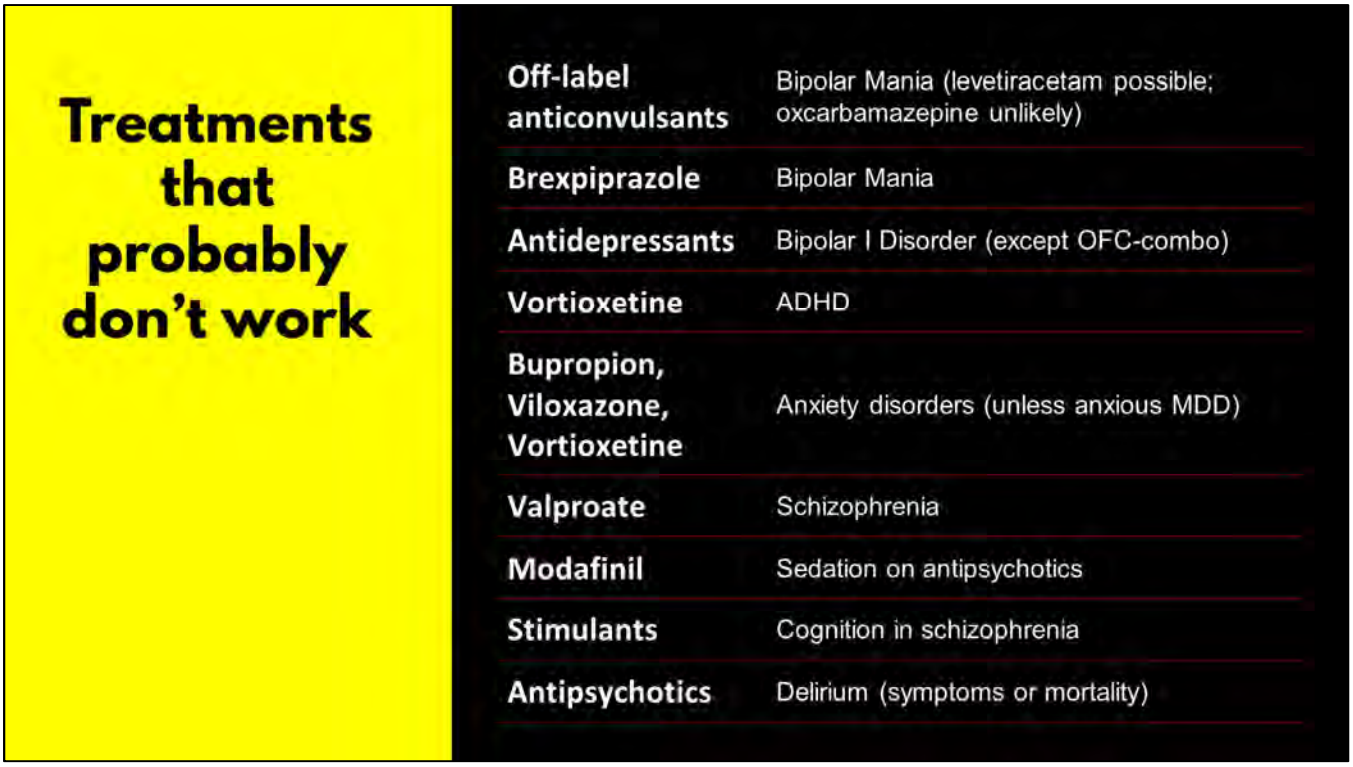
Mirtazapine looked positive in a 2022 meta-analysis from JAMA, but in that analysis all the well-designed, large trials were negative, and most of the positive ones were small in size.

However, there are exceptions where these strategies might work. The next page shows how they might be personalized, with the caveat that this is based on secondary analysis of the large trials - data fishing for a positive signal.

Obesity (BMI ≥ 30) Inflammation (CRP ≥ 3) Nicotine cessation	Anxious Depression	Anxious Depression (as first-line monotherapy)
Bupropion	**Mirtazapine**	**Buspirone**
Methylphenidate: elderly w/apathy, medical d/o Lisdexamfetamine Depression w/ executive dysf	Chronic Depression (over 8 years)	
Stimulants	**Lamotrigine**	

These are subtypes where the augmentation may have benefits (most are based on secondary findings)

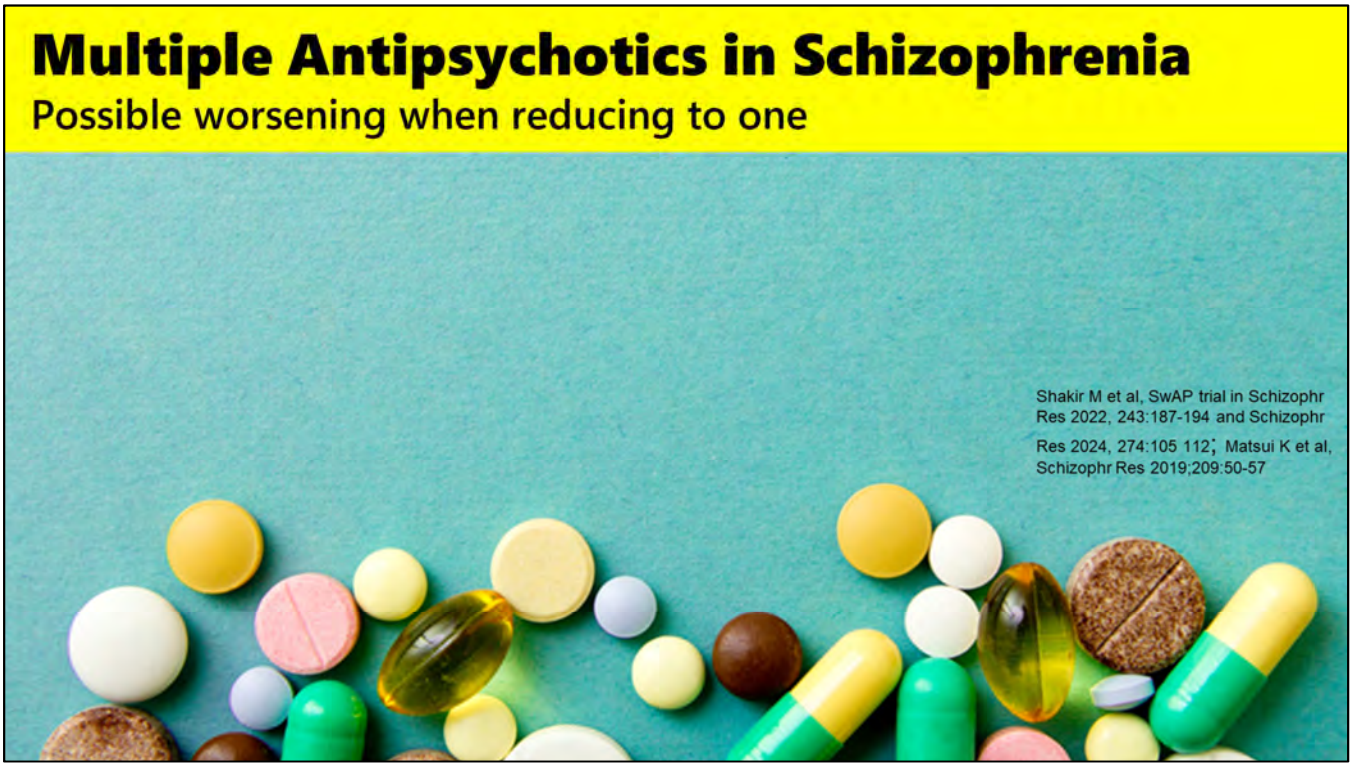
REFERENCES: Richards C, et al. J Affect Disord 2016;206:151-160; Ravindran AV et al, J Clin Psychiatry. 2008;69(1):87-94; Patkar AA et al, J Clin Psychopharmacol. 2006;26(6):653-656; Trivedi MH et al, J Clin Psychiatry. 2013;74(8):802-809.



DELIRIUM: Cochrane review of non-ICU patients (9 trials, 727 participants) found antipsychotics did not reduce delirium severity, resolve symptoms, or alter mortality compared to placebo or nonantipsychotic drugs (very low to low-quality evidence.

Disorders where meds usually fail

	POSSIBLE EXCEPTIONS
Pediatric MDD	Fluoxetine
Anorexia	Zinc
Autism	Aripiprazole and risperidone for behavioral aggression, memantine, some CAMs (folinic acid, omega-3, NAC, probiotics)
Trichotillomania	Memantine, NAC
Cognition in chronic psych disorders	
Agitation in dementia	Brexpiprazole
Psychosis in dementia	Small effect with antipsychotics



6 randomized trials have tested reduction to monotherapy in schizophrenia. Some show better psychotic outcomes with monotherapy (in those on long-term inpatient units, many on clozapine); others show no difference or a possible low risk of worsening. Most document lower weight, akathisia, parkinsonism, dyskinesia. When patients with schizophrenia take clozapine, polypharmacy goes down (Ochi S et al, Int J Neuropsychopharmacol 2022;25(10):818-826); same is true for bipolar with lithium. In contrast, observational data suggest possible benefit with aripiprazole-clozapine combination.


Risky and Irrational Combinations



Anticholinergics

TABLE 17-2. The Human Cost of Anticholinergic Drugs

Anticholinergic Effect	Why it Matters
Dry mouth	Tooth decay, gum inflammation and ulceration, halitosis; poor dental hygiene is a risk factor for depression and dementia
Constipation	Bowel obstruction with potentially fatal paralytic ileus and sepsis
Urinary retention	Urinary tract infections, renal or bladder damage
Dilated pupils	Acute narrow-angle glaucoma, traffic accidents, falls
Impaired papillary accommodation	Inability to read fine print
Increased heart rate	Increased risk of cardiac arrest
Decreased sweating	Hyperthermia
Decreased bronchial secretions	Mucous plugging of small airways, which worsens respiratory illnesses like asthma and bronchitis
Cognitive impairment	Poor memory and concentration; delirium; increased risk of dementia

Aiken C et al, Prescribing Psychotropics, 2020

acbcalc.com

Aiken C et al, Prescribing Psychotropics, 2020

	Anticholinergic Burden			
	Very Low (0)	**Low (1)**	**Medium (2)**	**High (3)**
Antidepressants		Bupropion Citalopram Fluoxetine Fluvoxamine Selegiline Trazodone Venlafaxine	Desipramine Sertraline Trimipramine	Amitriptyline Clomipramine Doxepin Imipramine Nortriptyline Paroxetine
Antipsychotics	Brexpiprazole Cariprazine Lumateperone Lurasidone Paliperidone Thiothixene Ziprasidone	Aripiprazole Asenapine Haloperidol Iloperidone Risperidone	Loxapine Pimozide Prochlorperazine	Chlorpromazine Clozapine Fluphenazine Olanzapine Perphenazine Quetipaine Thioridazine
Other		Alprazolam Clorazepate Diazepam Pramipexole Diphenhydramine	Amantadine Carbamazepine Oxcarbazepine	Benztropine Doxylamine (Unisom) Hydroxyzine

In 2020 the FDA issued a specific warning about combining clozapine with anticholinergics because they increase the risk of intestinal ileus, a potentially fatal form of constipation, 6-fold.. Higher numbers on acbcalc predict falls and mortality, cognitive decline.

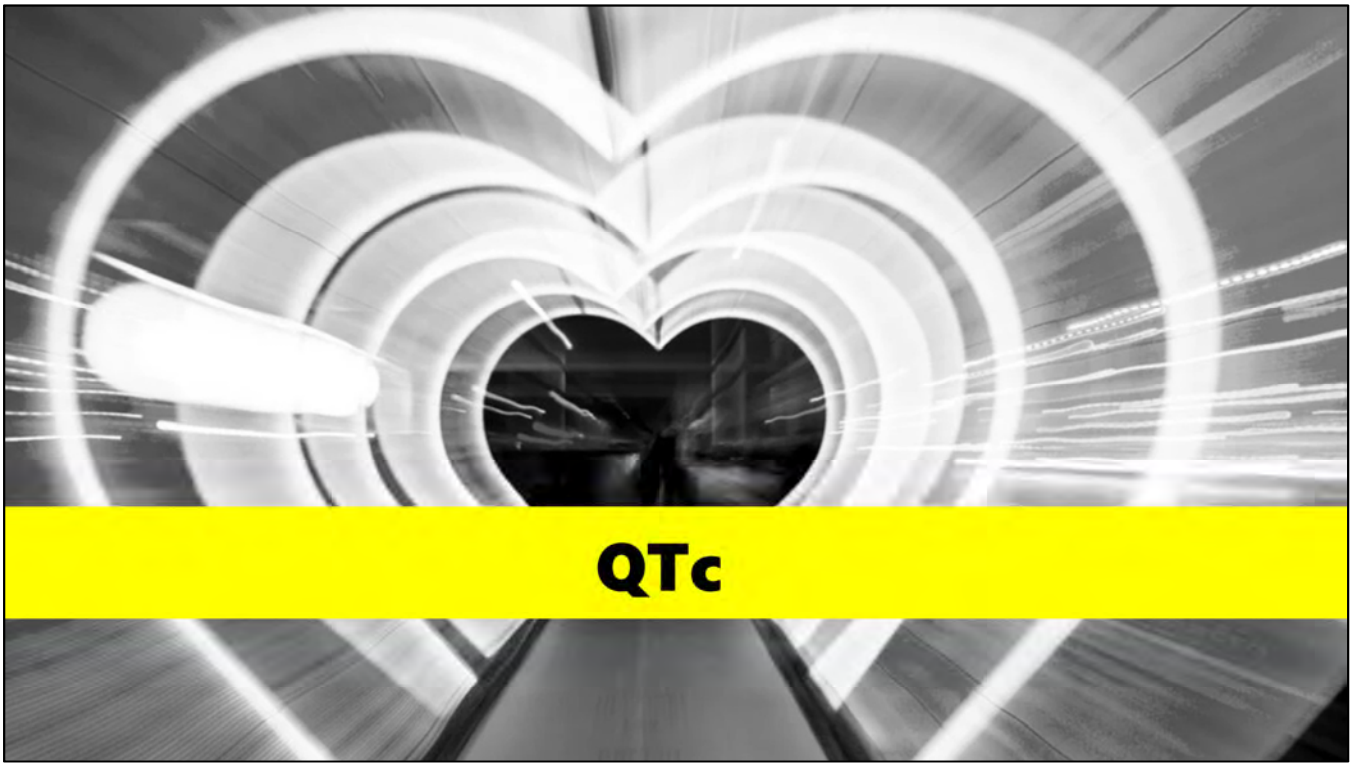
Taper slowly (2-4 weeks)

Avoid anticholinergic rebound:

Anxiety, insomnia, confusion, EPS, sweat, salivation, diarrhea



Somatic/autonomic: Nausea, vomiting, diarrhea, diaphoresis, hypersalivation, lacrimation, urinary urgency, bradycardia, hypotension
Neuropsychiatric: Anxiety, agitation, insomnia, psychomotor retardation, confusion, psychotic exacerbation
Movement disorders: Worsening extrapyramidal symptoms, dyskinesias, catatonia (in severe cases)


QTc

crediblemeds.org

Aiken C et al, *Prescribing Psychotropics*, 2020

Risk of Torsades de Pointes With Psychiatric Medications

	Conditional (Low) Torsades Risk	Possible Torsades Risk	Known Torsades Risk	Only Dangerous in Congenital Long QT
Antidepressants	Amitriptyline Clomipramine Doxepin Fluoxetine Fluvoxamine Paroxetine Sertraline Trazodone	Desipramine Imipramine Maprotiline Mirtazapine Nortriptyline Trimipramine Venlafaxine	Citalopram Escitalopram	
Antipsychotics	Olanzapine Quetiapine Risperidone Ziprasidone	Aripiprazole Asenapine Clozapine Iloperidone Lumateperone Lurasidone Perphenazine Paliperidone Pimavanserin Promethazine	Chlorpromazine Haloperidol Pimozide Thioridazine	
ADHD		Atomoxetine		Psychostimulants
Other	Amantadine Chloral hydrate Diphenhydramine Galantamine Hydroxyzine	Lithium Buprenorphine Deutetrabenazine Valbenazine Tetrabenazine Dextromethorphan/ Quinidine Memantine Pitolisant Vardenafil	Donepezil Ondansetron Methadone	

When to Worry

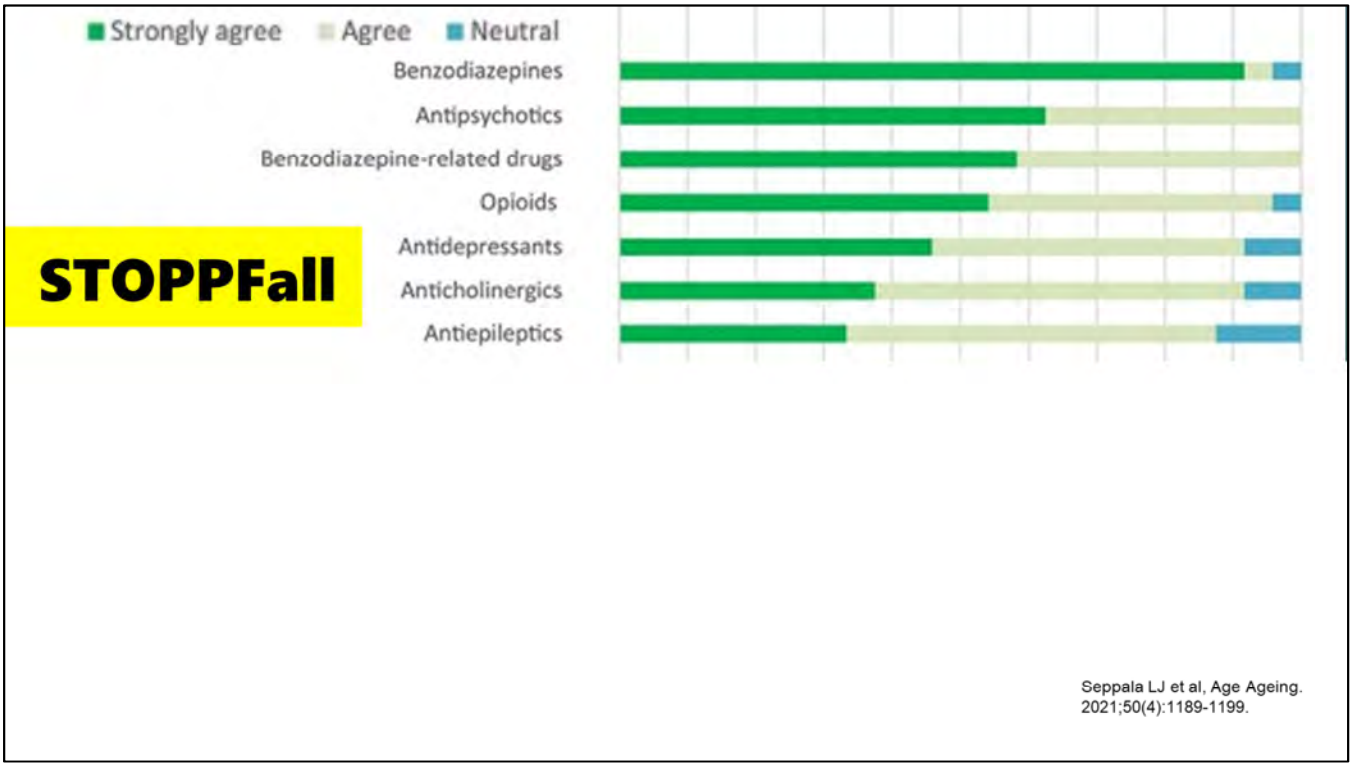
Electrolyte imbalance, heart disease, older age, cocaine/stim misuse



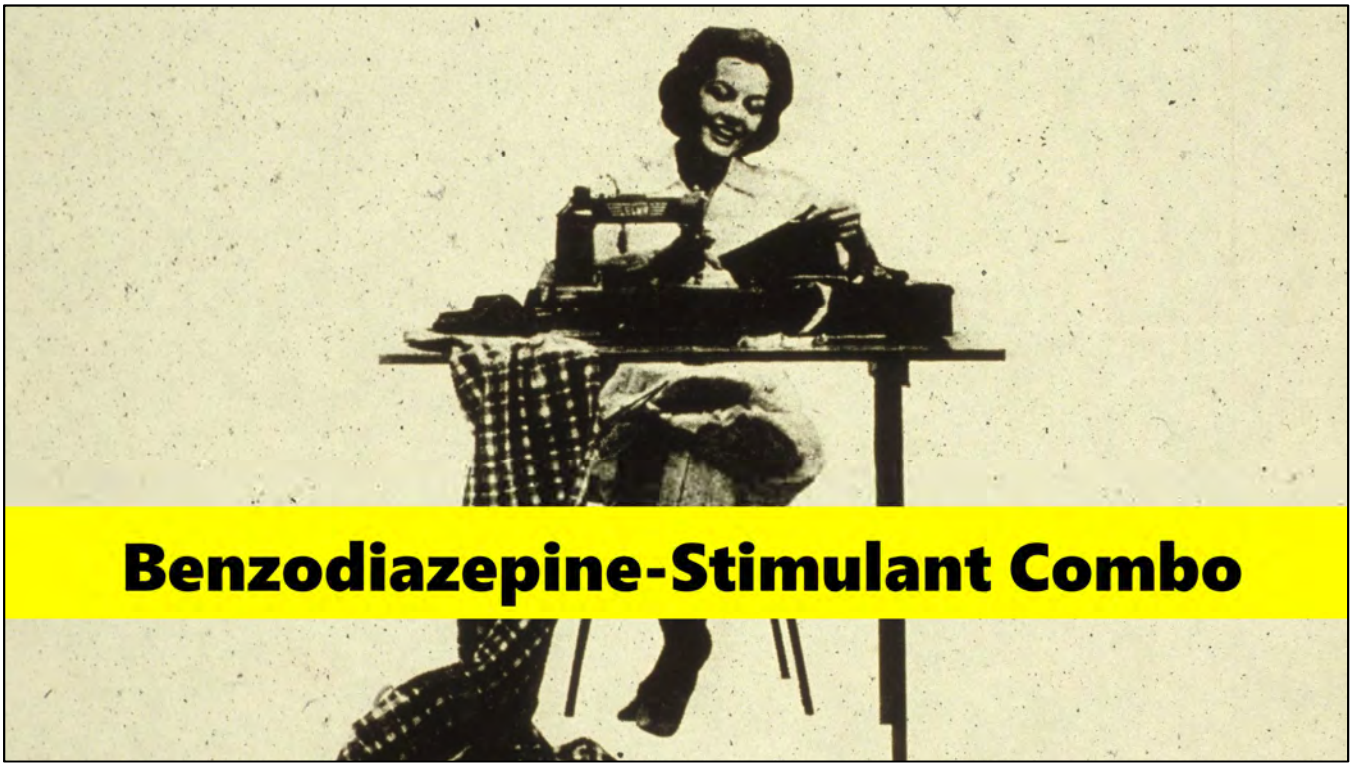
Torsades de pointe very rare unless risks present. The big three are low potassium, low magnesium, and heart disease (specifically, low left ventricular ejection fraction, left ventricular hypertrophy, ischemia, and slow heart rate). Other risks include older age, female gender, and recreational use of cocaine or stimulants.

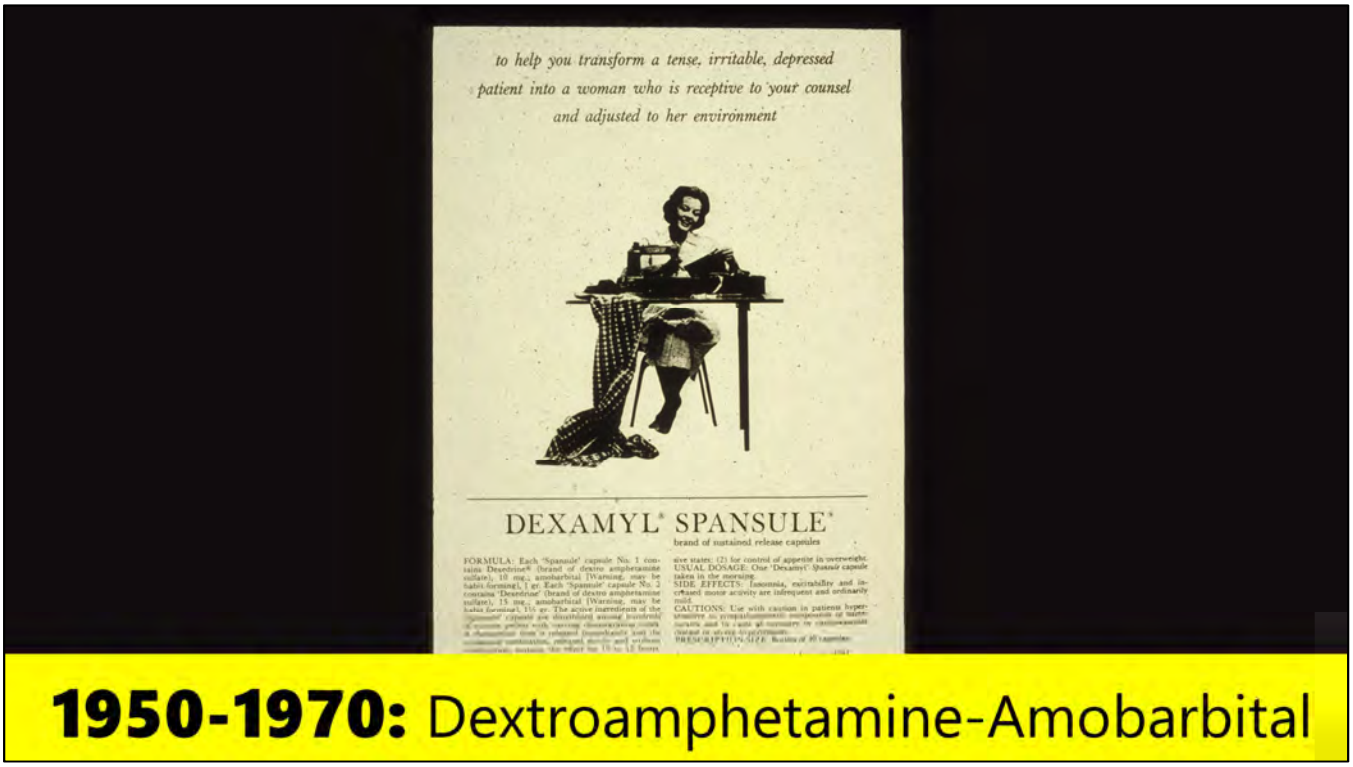
Falls





Shows expert consensus on meds that increase fall risk. Also bupropion.

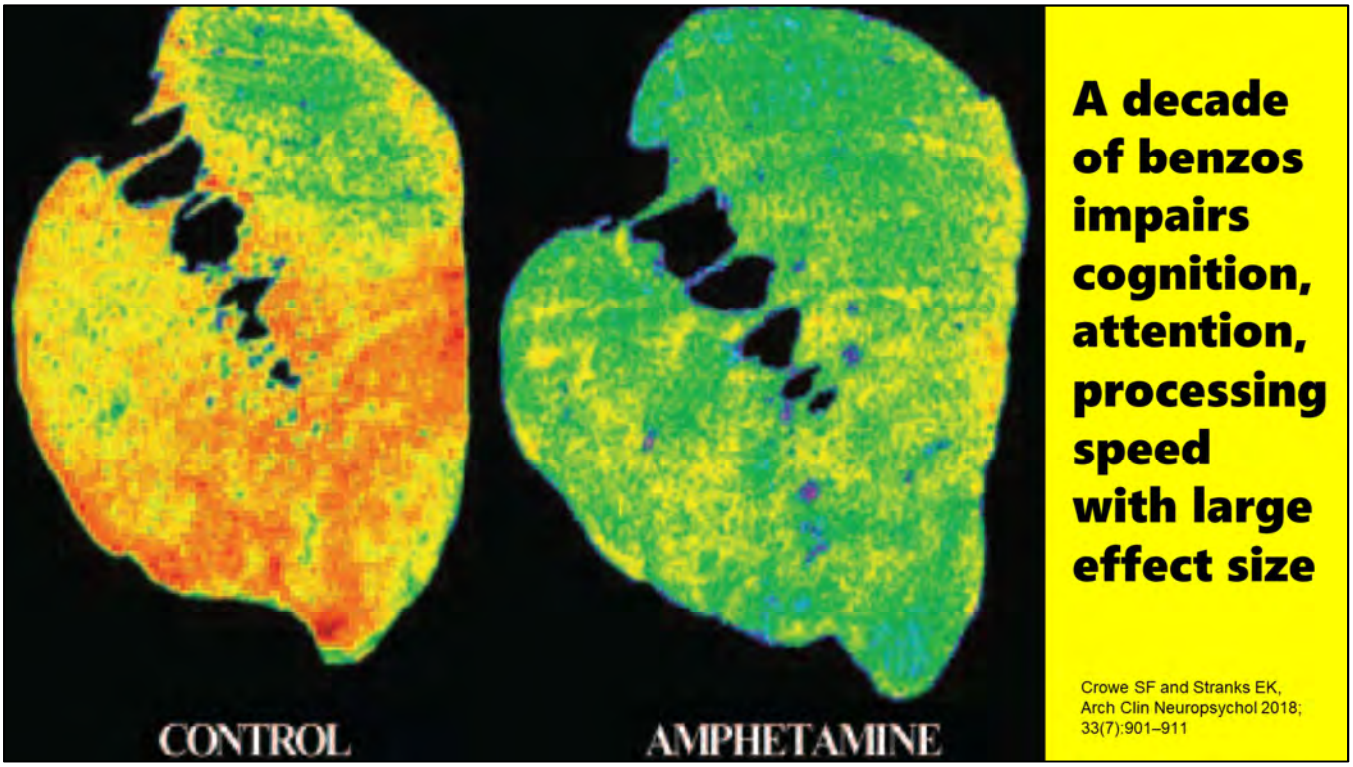

Benzodiazepine-Stimulant Combo



First “mood stabilizer”. Benzos tested for “hyperkinetic” disorder in 1960s but use fell out of favor due to cognitive side effects. Also used to reduce side effects (anxiety, insomnia) on stimulants.



Most (60%) from PCPs, 30% from psychiatrists; REF: Borrelli EP et al, *J Manag Care Spec Pharm* 2022;28(1):58–68



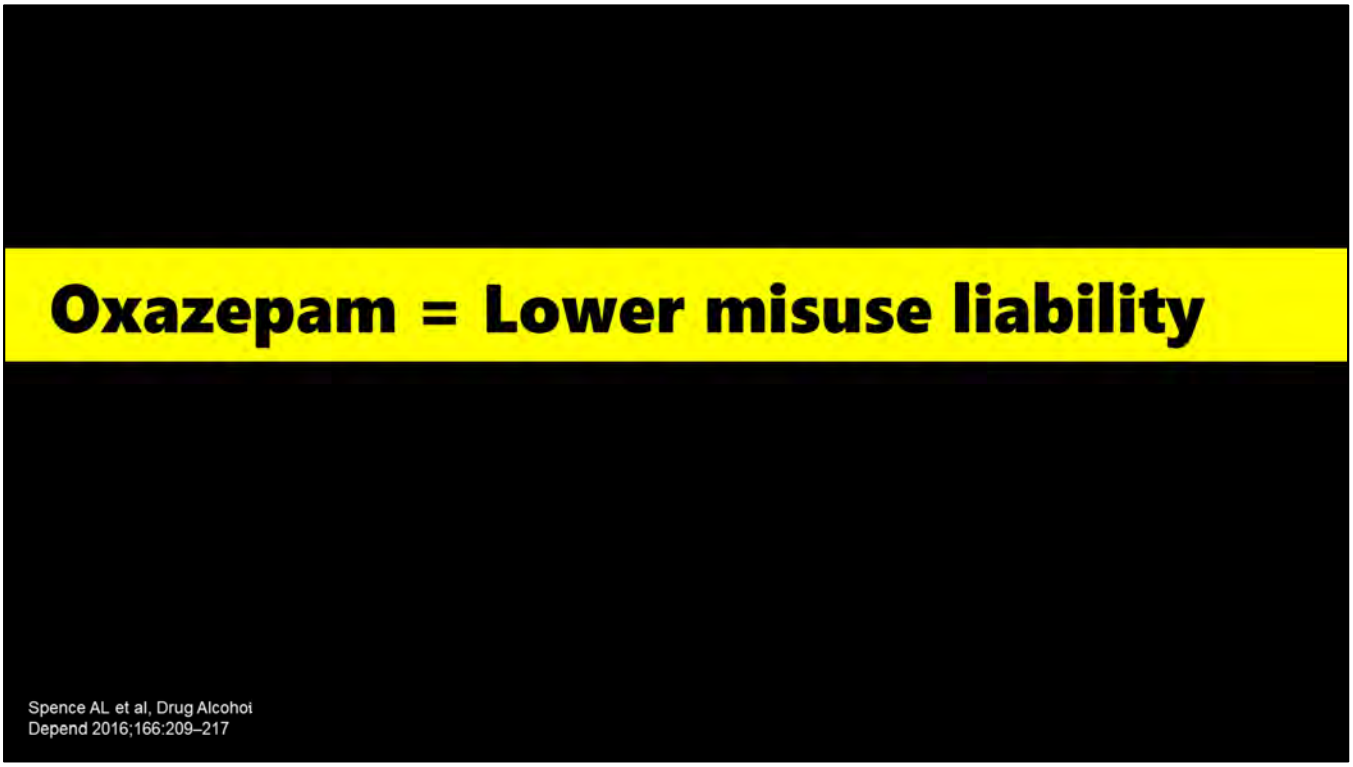
Synergestic neurotoxicity with benzos and stimulants. The picture shows toxicity to dopaminergic neurons with 60 mg/d of Adderall in a primate brain (most toxicity trials show problems at higher doses).



Methylphenidate, not amphetamines, reduce accident risk in ADHD, PMID: 27006144, PMID: 16950962; possible benefit: PMID: 18815438



Benzos do not increase stimulant addiction, but stimulants (amphetamines) can lead to benzo abuse. Benzos dampen the rewarding effects of stimulants.

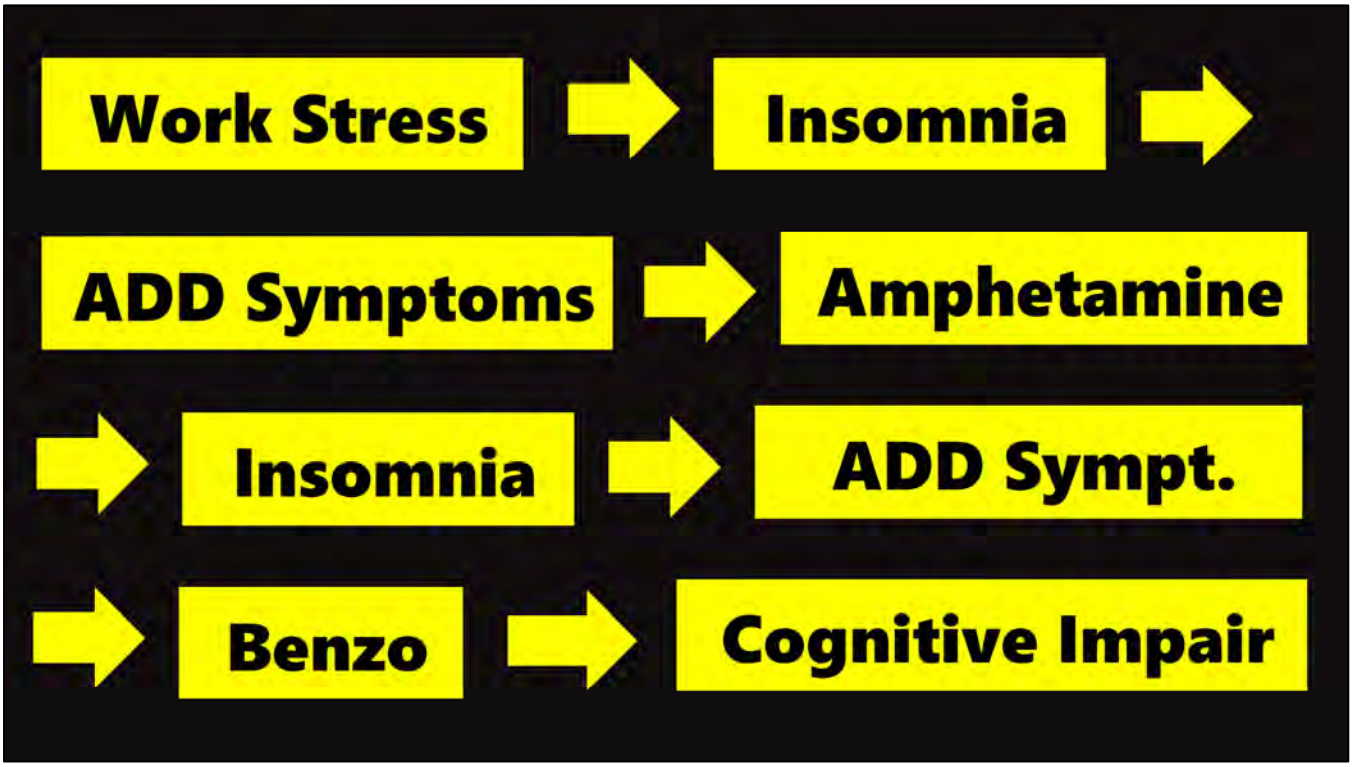


Oxazepam raises neurosteroids that block the rewarding properties of drugs of abuse. Oxazepam also has a lower abuse liability than most benzodiazepines when used on its own, and lower OD risk, because of its delayed time to onset (60 min vs 15-30 min) and short half-life.

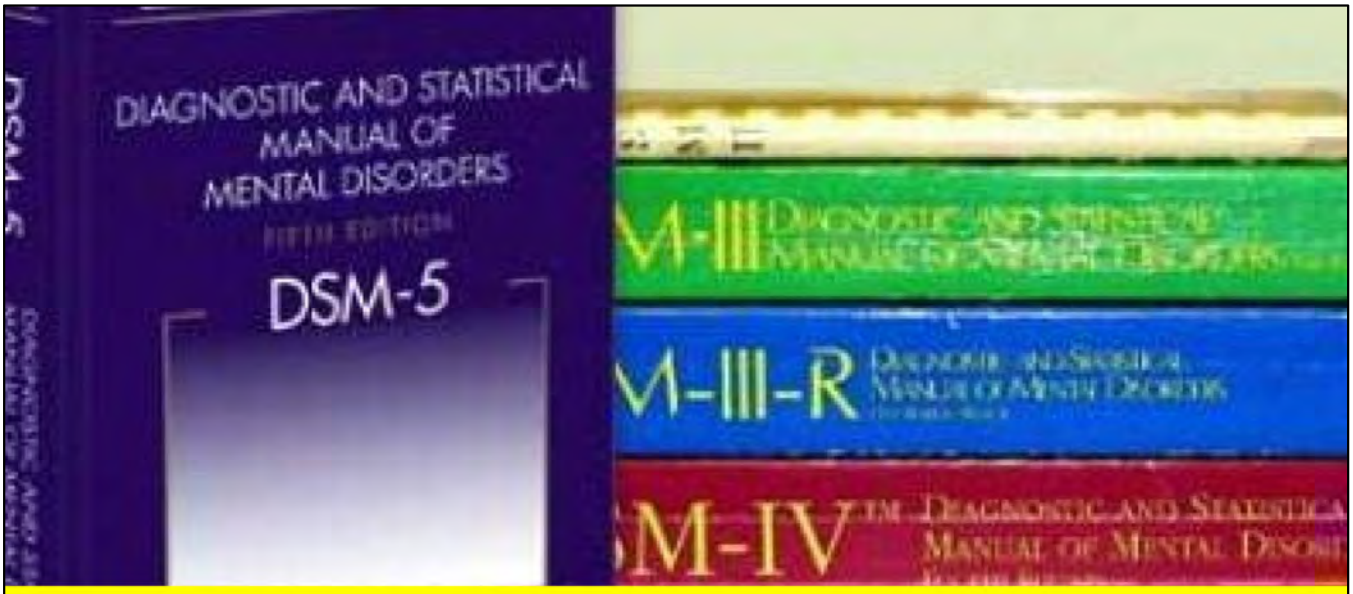
2. LIFESTYLE USE: Taper gradually



When patients are prescribed stimulants+benzos without a clear diagnosis that indicates them (ie, for “lifestyle” or stress), taper gradually as the use is not indicated and should not be long-term.

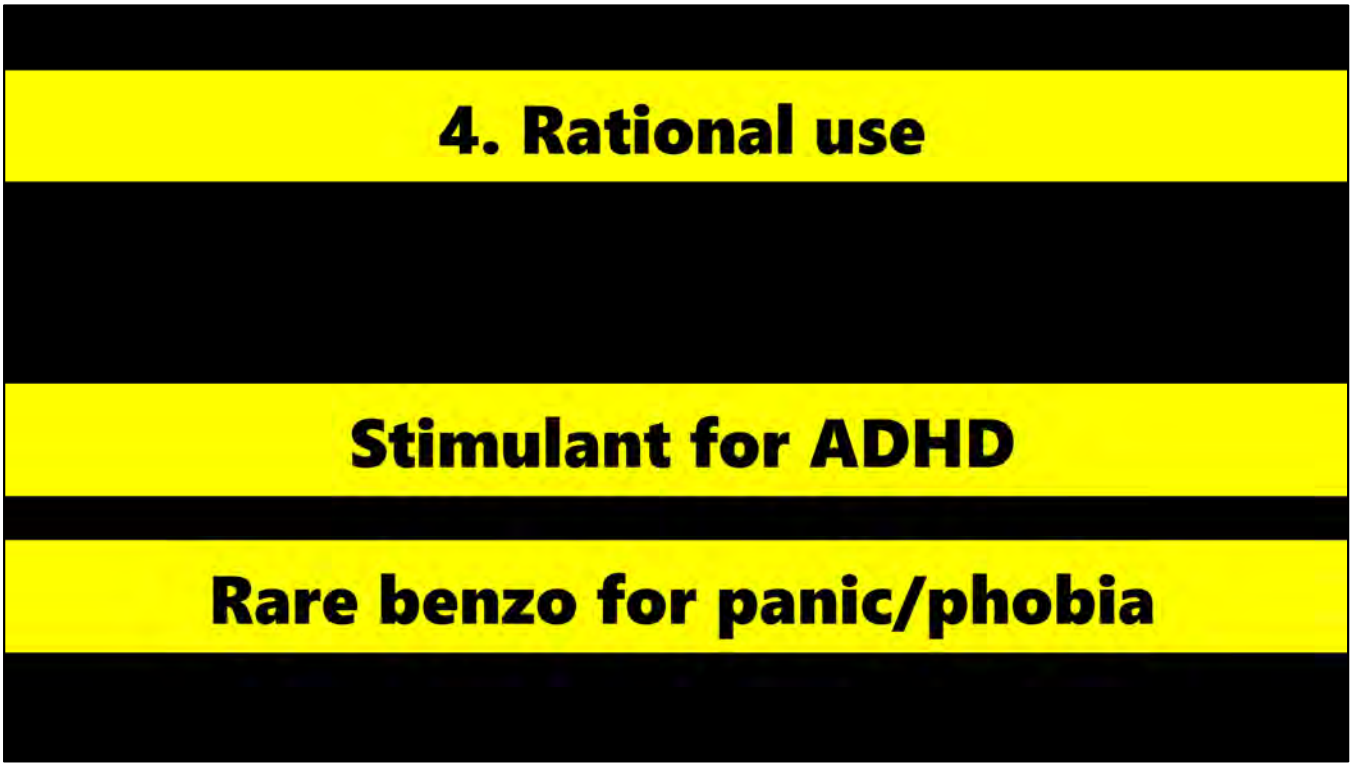


Majority (93% to 95%) of “adult onset ADHD” are better explained by sleep disorders, substance use disorders, or another psychiatric disorder; also sleep apnea common in ADHD (20-30%). REF: Sibley MH et al, Am J Psychiatry. 2018;175(2):140-149; Lopez R et al, Psychiatry Res. 2017;257:238-241.

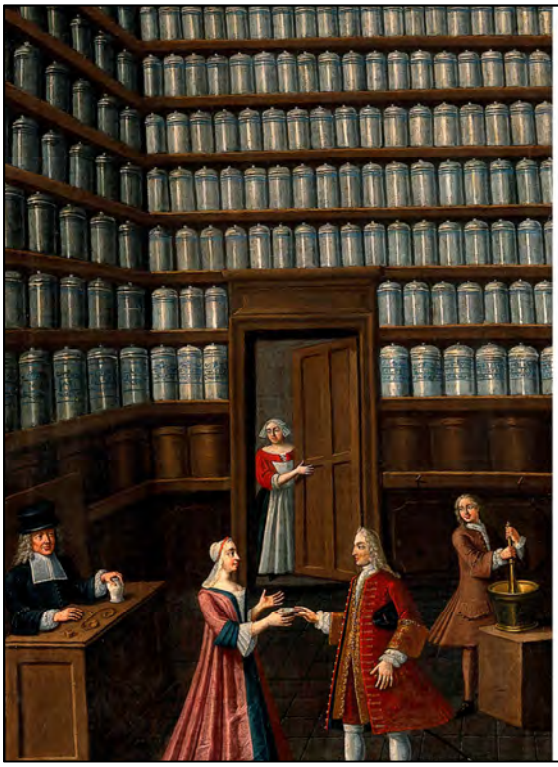


3. COMPLEX COMORBIDITY: Taper gradually

Whe patients are taking non-indicated stim/benzo combo and have complex psychiatric comorbidities, it is irrational but not acutely dangerous; taper gradually.



The treatment literature on benzo/stim combos is limited to one case report of comorbid panic disorder with ADHD, PMID: 10570768



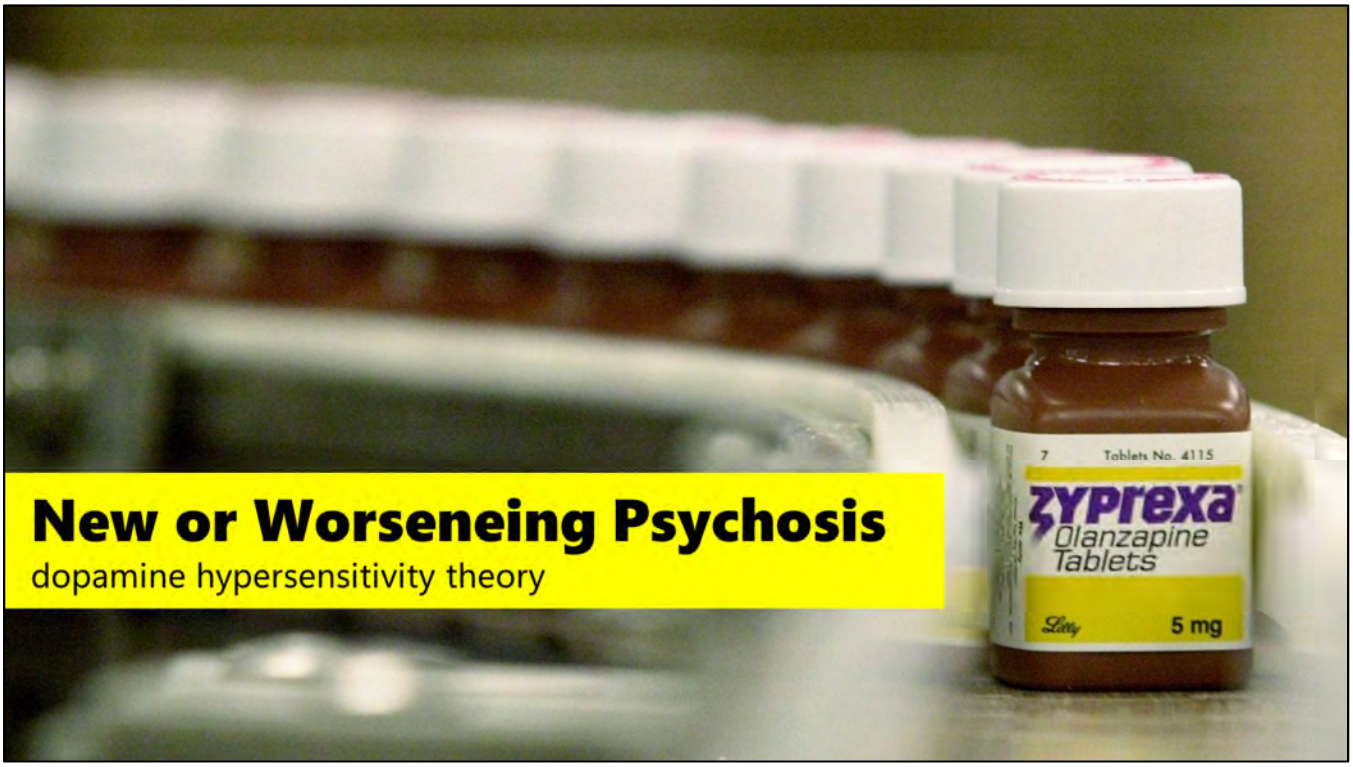
How to Taper

TABLE 45-1. Withdrawal Symptoms by Medication Class

Medication	Withdrawal Symptoms
Antipsychotics	**Psychiatric:** Insomnia, anxiety, psychosis **Physical:** Tremor, headache, dizziness, nausea, tachycardia, akathisia, dyskinesias
Benzodiazepines	**Psychiatric:** Anxiety, insomnia, nightmares, irritability, sensory changes, dissociation, paranoia **Physical:** Tremor, tinnitus, headache, dizziness, muscle spasms, GI distress, palpitations, seizures
Bupropion	**Psychiatric:** Anxiety, insomnia, irritability **Physical:** Fatigue, headache, myalgias, restlessness
Buspirone and gepirone	None known
Mirtazapine	**Psychiatric:** Depression, anxiety, insomnia **Physical:** Itch, appetite loss
Modafinils	**Psychiatric:** Depression, anxiety, hypersomnia, brain fog **Physical:** fatigue, headaches, sweats, chills
SSRIs and SNRIs	**Psychiatric:** Dysphoria, anxiety, mania, insomnia, irritability, brain zaps, sensory changes, dissociation **Physical:** Tremor, sweats, myalgias, restlessness, headache, chills, GI distress, tinnitus
Stimulants	**Psychiatric:** Depression, irritability, anxiety, insomnia, nightmares, hypersomnia, brain fog, agitation **Physical:** Crashing fatigue, dystonic movements, increased appetite

Anticholinergics: Cholinergic Reboud

Aiken C, *Difficult to Treat Depression* book (2025)



New or Worseneing Psychosis

dopamine hypersensitivity theory


Dysphoric, anxious, irritable.
Brain zaps, imbalance, tinnitus, chills, myalgia
SSRI and SNRI Withdrawal Syndrome

Worse with paroxetine and venlafaxine



SSRI and SNRI Withdrawal Syndrome

Worse if over two years on medication



SSRI and SNRI Withdrawal Syndrome

A Hyperbolic Taper for SSRIs

1. Lower to the Minimum Effective Dose

Reduce the dose to the minimum suggested in Table 46.1 if not already there (eg, citalopram 20 mg). At this stage, the dose can be reduced linearly (eg, by 5–10 mg) because the main risk is depressive relapse, not serotonin withdrawal. Lowering every two to four weeks is reasonable for most patients, but longer intervals may be needed for those with a history of withdrawal problems or a long duration of treatment.

2. Assess Baseline Symptoms

Check if the patient is having any symptoms that correspond to SSRI withdrawal symptoms at baseline.

3. Lower For One Month and Reassess

Now move to the first tapering dose in the table (eg, citalopram 10 mg). Monitor for withdrawal symptoms throughout the taper and adjust the rate of taper based on withdrawal symptoms.

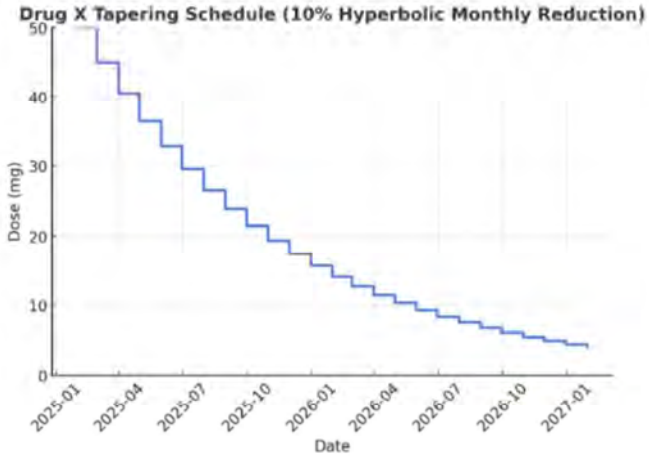
4. Start the Long-Tail Taper

The doses for each step of the final taper are listed in Table 46.1 (eg, citalopram 5 mg, then 3.4 mg). How quickly you go down at each step depends on how sensitive the patient is to withdrawal. Your assessment of their symptoms at baseline and one month later will give you a sense of that. At a minimum, allow two weeks between each step; four weeks is a rough average. Patients who experience withdrawal effects benefit from making smaller reductions at each step rather than spacing out the time in between dose reductions.

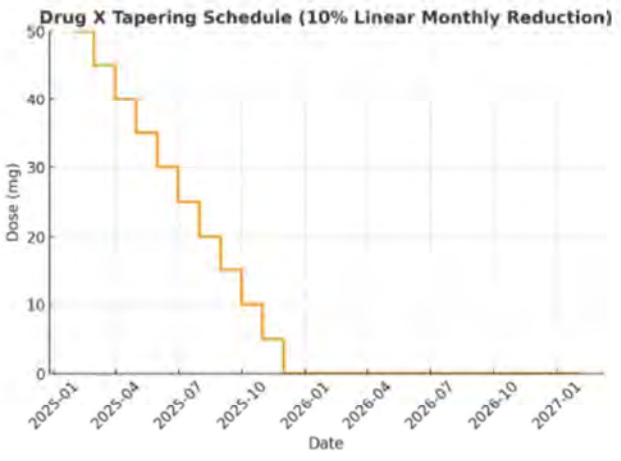
TABLE 46-1. Tapering Doses and Liquid Conversions for Common SSRIs

Medication	Minimum Daily Dose*	Tapering Doses (mg/day)	Liquid Conversion (mL/day)
Citalopram	20 mg	10 mg→ 5→ 3.4→ 2.3→ 1.5→ 0.8→ 0.4→ stop	2 mg/mL: 5 mL→ 2.5→ 1.7→ 1.2→ 0.8→ 0.4→ 0.2→ stop
Escitalopram	10 mg	5 mg→ 2.7→ 1.7→ 1.2→ 0.7→ 0.4→ 0.2→ stop	1 mg/mL: 5 mL→ 2.7→ 1.7→ 1.2→ 0.7→ 0.4→ 0.2→ stop
Fluoxetine	20 mg	8.5 mg→ 4.5→ 2.7→ 1.7→ 1.0→ 0.6→ 0.3→ stop	4 mg/mL: 2.1 mL → 1.1→ 0.7→ 0.4→ 0.3→ 0.2→ 0.1→ stop
Fluvoxamine	50 mg	25 mg→ 15→ 10→ 8→ 5→ 2→ 1→ stop	No liquid (use 25 mg tabs or compounding pharmacy)
Paroxetine	20 mg	11.4 mg→ 7.4→ 5.0→ 3.4→ 2.2→ 1.3→ 0.6→ stop	2 mg/mL: 5.7 mL → 3.7→ 2.5→ 1.7→ 1.1→ 0.7→ 0.3→ stop
Sertraline	50 mg	25 mg→ 14→ 9.1→ 5.9→ 3.8→ 2.2→ 0.9→ stop	20 mg/mL: 1.3 mL → 0.7→ 0.5→ 0.3→ 0.2→ 0.1→ 0.05→ stop

*The minimum daily represents the dose that typically achieves 80% occupancy at the serotonin receptor. It roughly corresponds with the minimum effective dose for depression.



Hyperbolic taper



Linear taper

Home-made emulsions for micro-doses

psych-partners.com/microdosing

