

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.

Polypharmacy more common in...



Women



**Disabilities
Foster care
(children)**



Medicaid

CAM Therapy

Is it natural to the
body or common in
the diet?

Phytochemicals
vs
Nutraceuticals



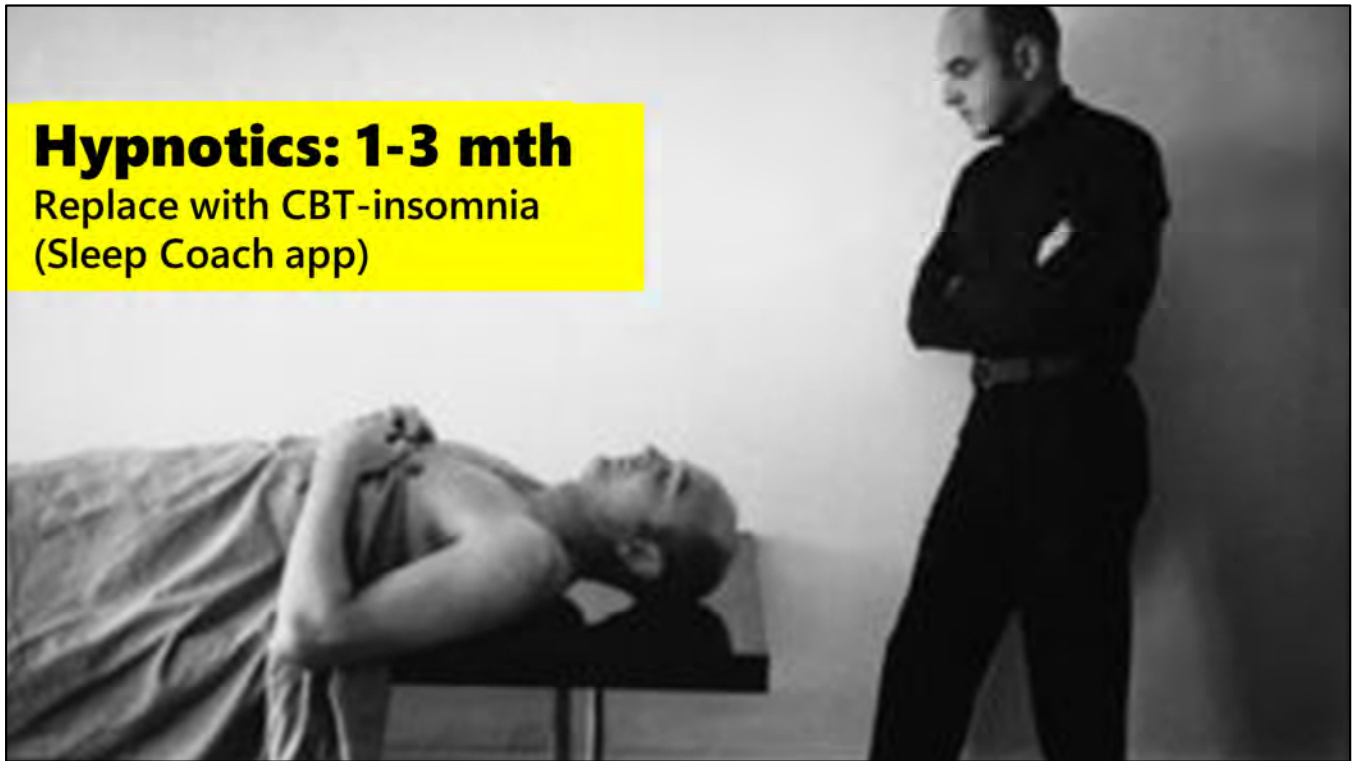
Phytochemicals are herbs and should be treated like medications. Nutraceuticals are safer and often have health benefits (they are already in the body), like vitamins, minerals, omega 3, probiotics.



Polypharmacy Prevention

Set an end date for short-term treatments





Hypnotics: 1-3 mth

Replace with CBT-insomnia
(Sleep Coach app)

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



Short-term Anxiolytics

2-6 weeks ideal for benzodiazepines in acute anxiety

Rapid anti-depressants:

Consider short-term (2-6 weeks)

OLD

- Benzodiazepines (alprazolam)
- Eszopiclone
- Pindolol
- Thyroid (T3)

NEW

- Bupropion-Dextromethorphan (Auvelity)
- Ketamine and Esketamine
- Zuranolone (for postpartum)
- *Future? Psychedelics*

Eszopiclone 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 Antidepressants

Taper after 6-12 mth remission in single episode depression,
or when used as adjunct in recurrent MDD or bipolar depression

In recurrent depression, continuing an antidepressant lowers relapse risk

- from 40% to 20%: in psychiatric randomized trials
- from 56% to 39%: in a real-world primary care randomized trial

Short-term Antipsychotic Augmentation

Taper after at least 6 months of remission in mood disorders

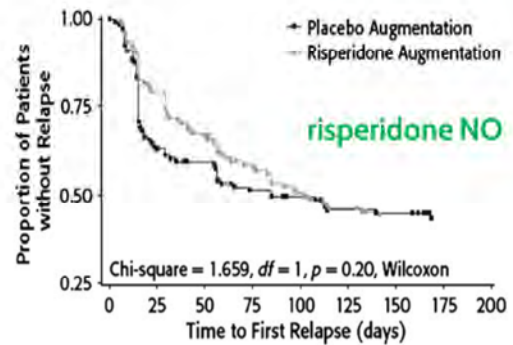
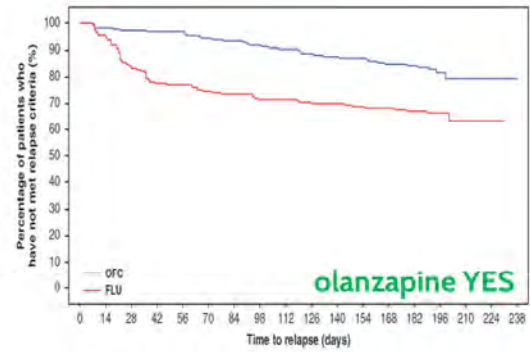
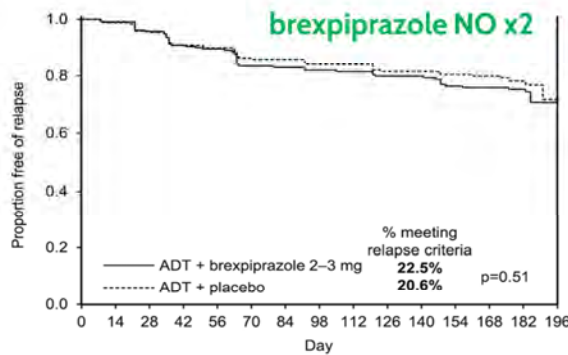


Yatham LN et al, Mol
Psychiatry 2016;21(8):1050-6

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)

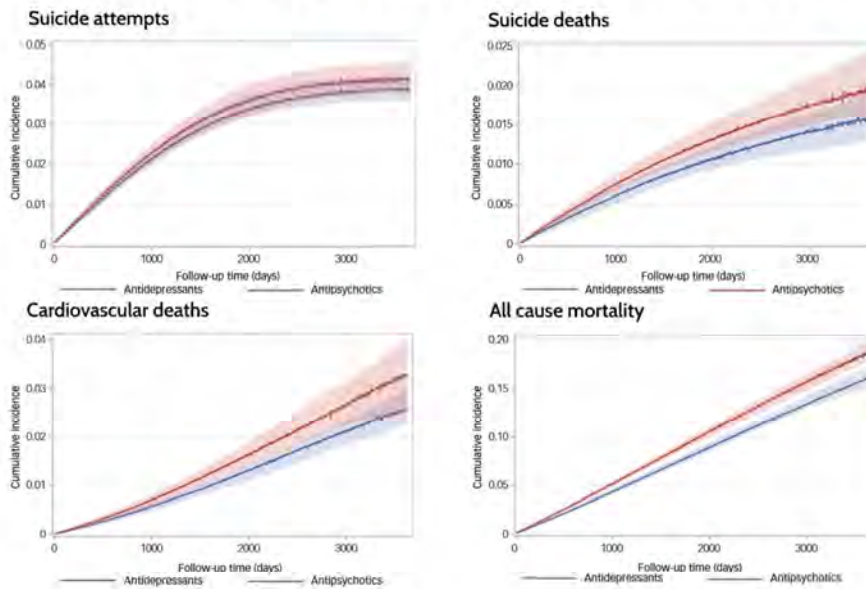
Do antipsychotics prevent unipolar depression?

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.

Antipsychotics don't prevent suicide, may raise mortality



Comparative cohort study of 79,898 patients with TRD.

Antipsychotic augmentation vs. matched controls who received third-line antidepressants

Tsai DH et al, Brit J Psychiatry 2025;1-9

Supported by other epidemiologic studies

Psychotic Depression

May require long-term antipsychotic augmentation

Relapse
20% vs 55%

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

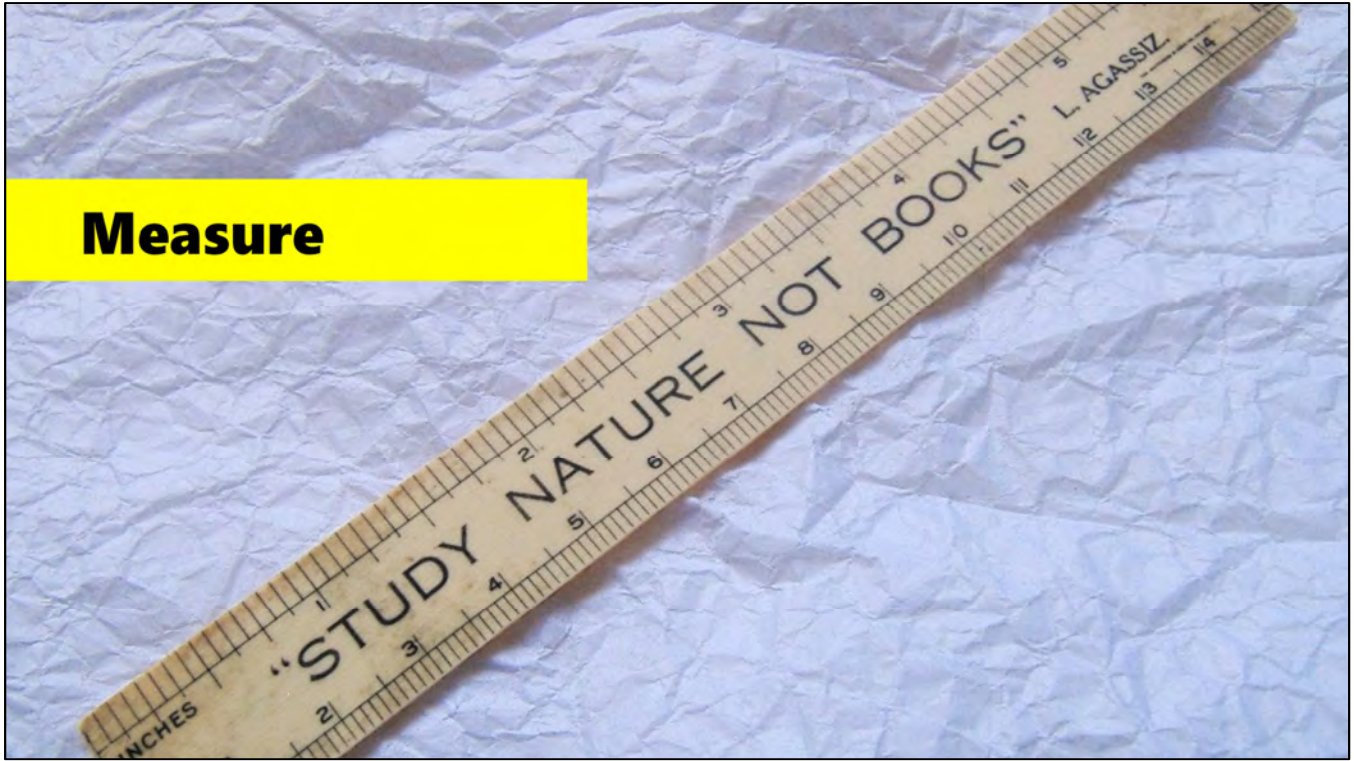




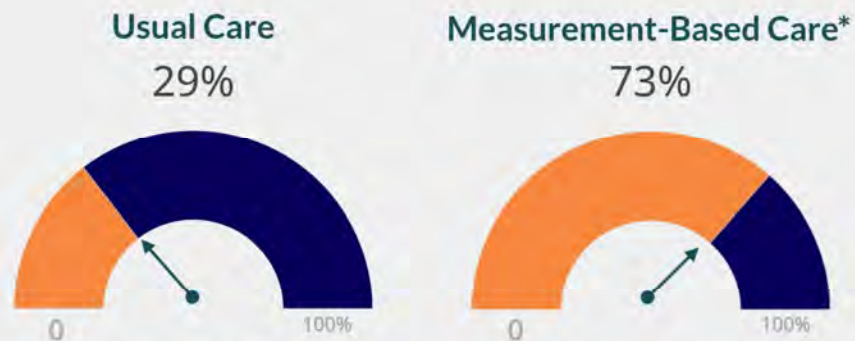
Time-limited stimulants

- Subthreshold ADHD
- ADHD that resolves in adulthood

Measure



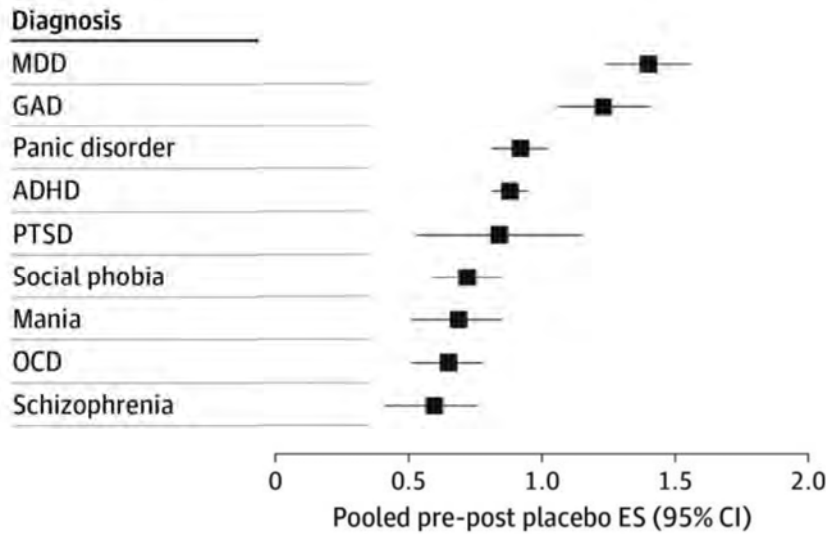
Regular Measurement Raises Remission in Depression



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 to 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

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)

Antipsychotic Max in Schizophrenia

Antipsychotic	95% effective dose	Response Plateau?
Aripiprazole	11.5 mg	Yes
Asenapine	15 mg	Yes
Brexipiprazole	3.4 mg	Yes
Haloperidol	6.3 mg	Yes
lloperidone	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 plateau and risks worsen above....

Amphetamines

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

Methylphenidates

- Methylphenidate 60 mg
- Dexmethylphenidate 30 mg



Antidepressant Augmentation

1	3	2
Bupropion	Mirtazapine	Buspirone
5	8_{small}	<i>About this Slide</i> Above each medication is the number of large, negative RCTs for antidepressant augmentation in MDD
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.

<p>Obesity (BMI \geq 30) Inflammation (CRP \geq 3) Nicotine cessation</p>	<p>Anxious Depression</p>	<p>Anxious Depression (as first-line monotherapy)</p>
<p>Bupropion</p>	<p>Mirtazapine</p>	<p>Buspirone</p>
<p>Methylphenidate: Elderly w/apathy, medical d/o</p> <p>Lisdexamfetamine Depression w/ executive dysf</p>	<p>Chronic Depression (over 8 years)</p>	<p><i>About this Slide</i></p> <p>Above each medication are populations where the augmentation strategy worked in secondary analyses</p>
<p>Stimulants</p>	<p>Lamotrigine</p>	

Treatments that probably don't work

Off-label anticonvulsants	Bipolar Mania (levetiracetam possible; oxcarbamazepine unlikely)
Brexipiprazole	Bipolar Mania
Antidepressants	Bipolar I Disorder (except OFC-combo)
Vortioxetine	ADHD
Bupropion, Viloxazone, Vortioxetine	Anxiety disorders (unless anxious MDD)
Valproate	Schizophrenia
Modafinil	Sedation on antipsychotics
Stimulants	Cognition in schizophrenia
Antipsychotics	Delirium (symptoms or mortality)

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	Brexiprazole
Psychosis in dementia	Small effect with antipsychotics

Multiple Antipsychotics in Schizophrenia

Possible worsening when reducing to one

Shakir M et al, SwAP trial in Schizophr Res 2022, 243:187-194 and Schizophr Res 2024, 274:105-112; Matsui K et al, Schizophr Res 2019;209:50-57



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.

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

		Anticholinergic Burden			
		Very Low (0)	Low (1)	Medium (2)	High (3)
acbcalc.com	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 Quetiapine Thioridazine
	Other		Alprazolam Clorazepate Diazepam Pramipexole Diphenhydramine	Amantadine Carbamazepine Oxcarbazepine	Benztrapine Doxylamine (Unisom) Hydroxyzine

Aiken C et al, Prescribing Psychotropics, 2020

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:

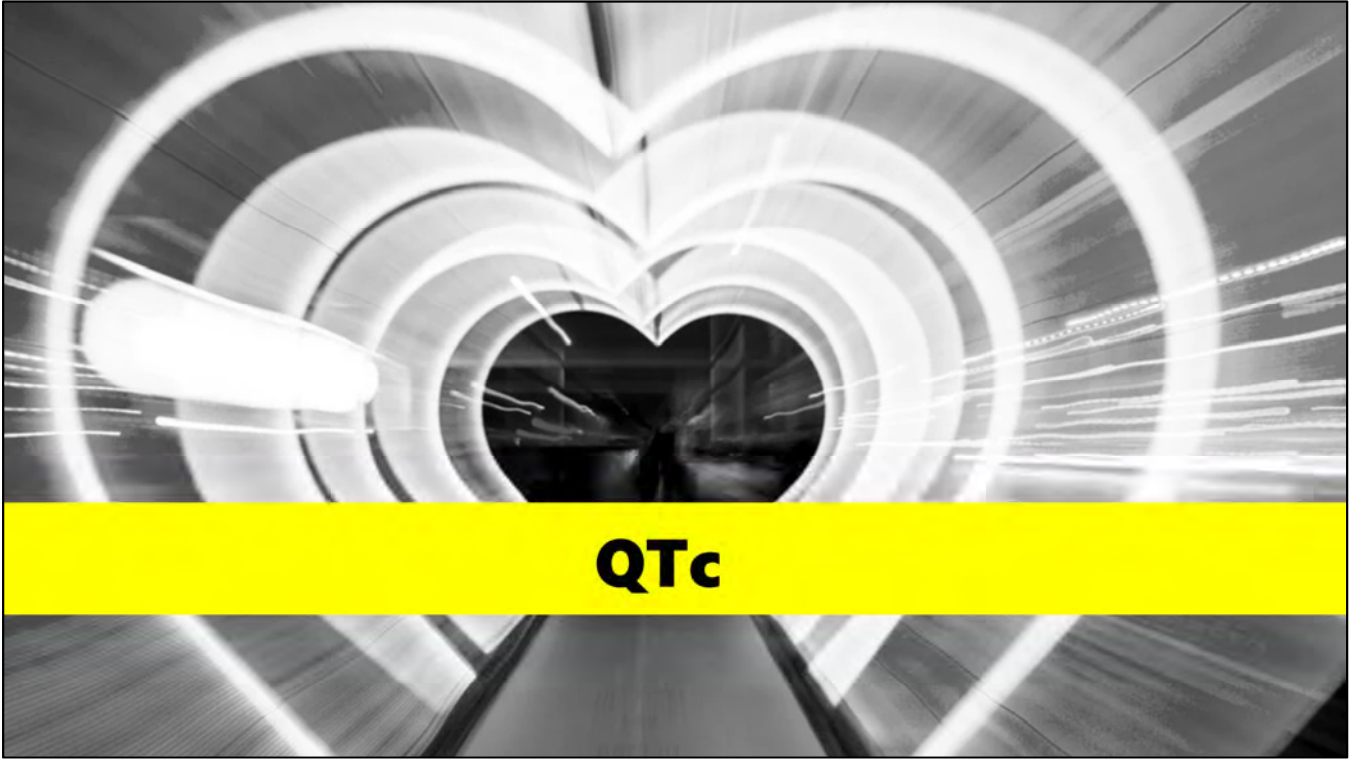
Anxiety, insomnia,
confusion, EPS,
sweat, salivation,
diarrhea



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

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	

Aiken C et al, Prescribing Psychotropics, 2020

When to Worry

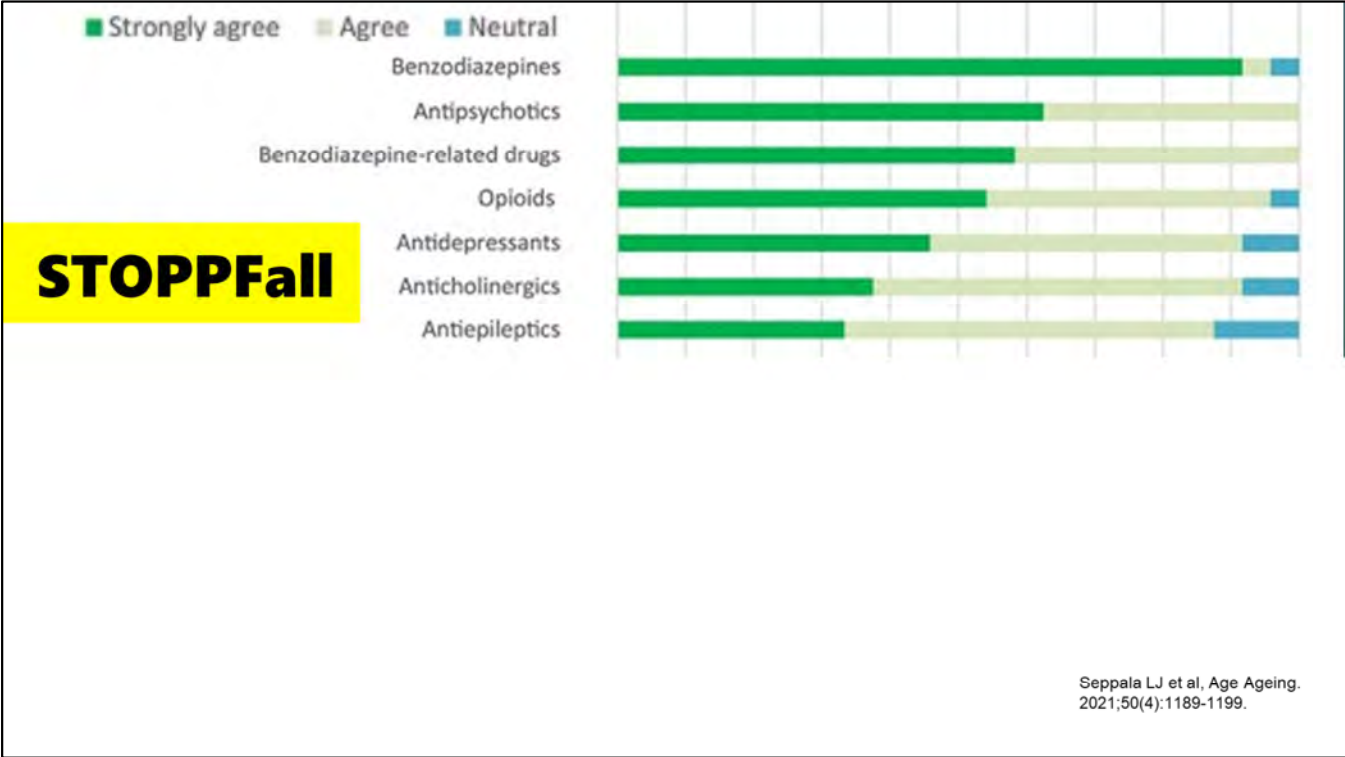
Electrolyte imbalance, heart disease, older age, cocaine/stim misuse



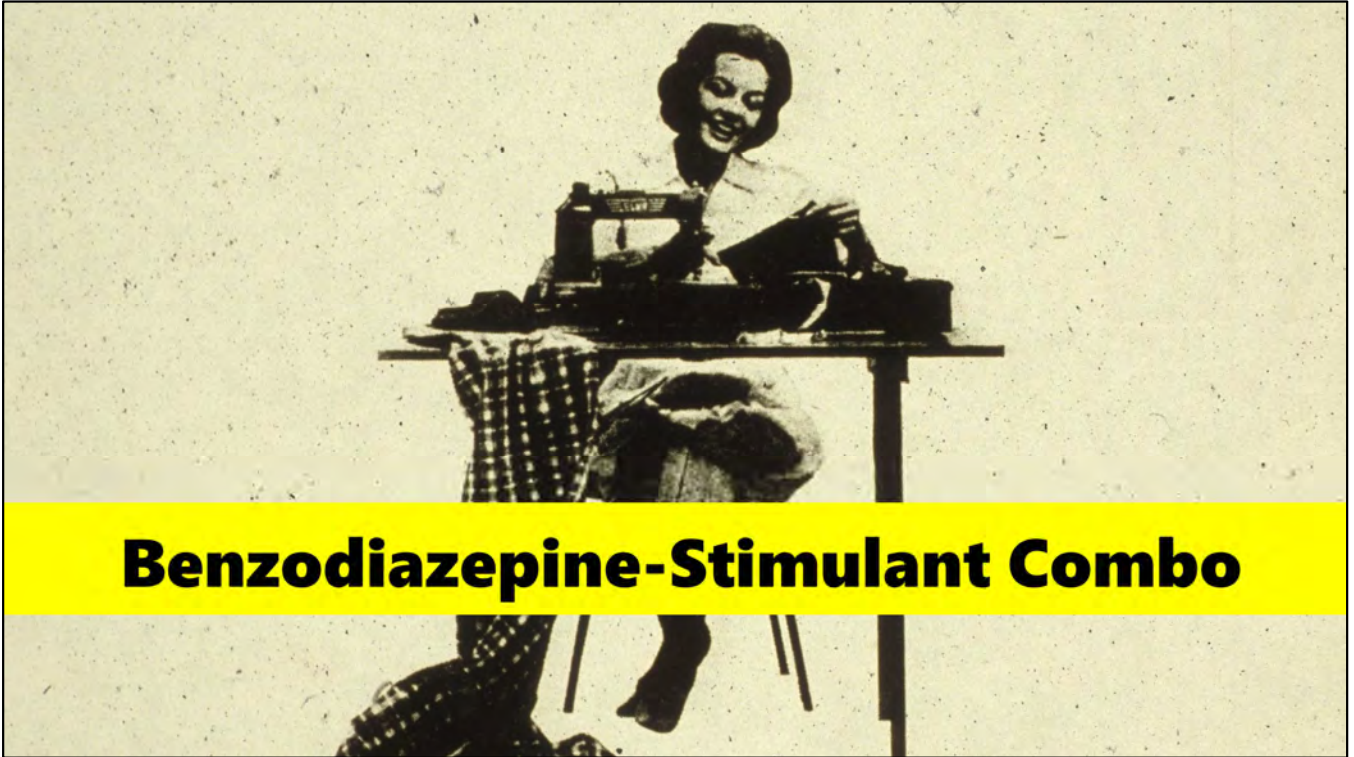
Torsades de pointe very rare unless risks present. The big three are low potassium, low magnesium, and heart disease (specifically, low left ventricular ejection fraction, left ventricular hypertrophy, ischemia, and slow heart rate). Other risks include older age, female gender, and recreational use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

Falls





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



Benzodiazepine-Stimulant Combo

*to help you transform a tense, irritable, depressed
patient into a woman who is receptive to your counsel
and adjusted to her environment*



DEXAMYL® SPANSULE®

brand of sustained release capsules

FORMULA: Each "Spansule" capsule No. 1 contains "Dexamyl" (brand of dextro-amphetamine sulfate), 10 mg., amobarbital (Waring, only to be taken during the day), 1 gr. Each "Spansule" capsule No. 2 contains "Dexamyl" (brand of dextro-amphetamine sulfate), 15 mg., amobarbital (Waring, may be taken during the day). The active ingredients of the "Spansule" capsules are distributed around a central core of porous gelatin with opening characteristics which in combination with a patented formulation yield the sustained, controlled, prolonged release and uniform concentration of the active ingredients.

over meals. (2) Eat control of appetite is unnecessary. **USUAL DOSAGE:** One "Dexamyl" Spansule capsule twice in the morning. **SIDE EFFECTS:** Tinnitus, excitability and increased motor activity are infrequent and ordinarily mild. **CAUTIONS:** Use with caution in patients hypersensitive to sympathomimetic amines or sulfonamide drugs or with a pre-existing condition. **PRESCRIPTION SIZE:** Boxes of 50 capsules.

1950-1970: Dextroamphetamine-Amobarbital

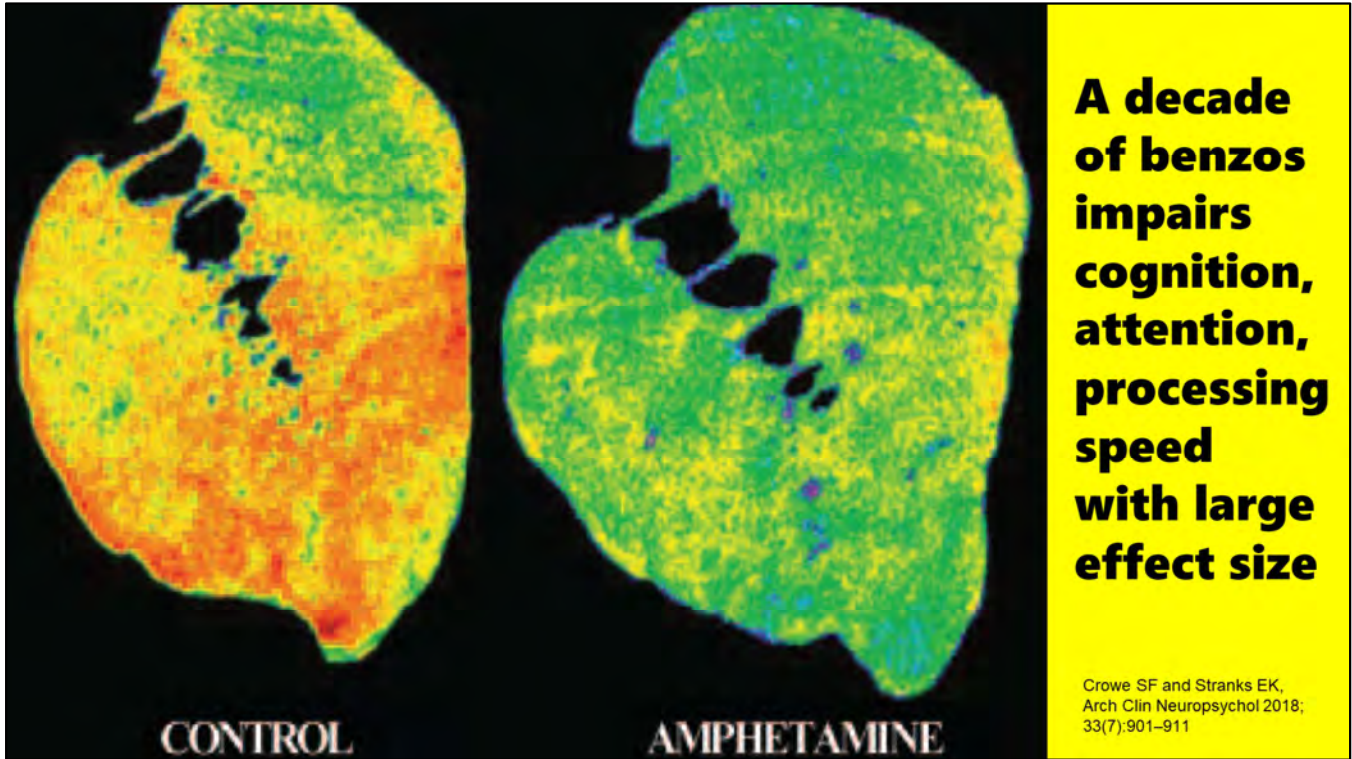
First "mood stabilizer". Benzos tested for "hyperkinetic" disorder in 1960s but use fell out of favor due to cognitive side effects. Also used to reduce side effects (anxiety, insomnia) on stimulants.

1 in 15 on benzo also on stimulant...



...in 2018, 40% higher than 2013

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



Synergistic 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).

Highest link to car accidents?



Amphetamine-Benzo

Zarkowski PA, Int J Psychiatry
Med 2020;55(2):82-104

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



1. MISUSE: Taper off now

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

Oxazepam = Lower misuse liability

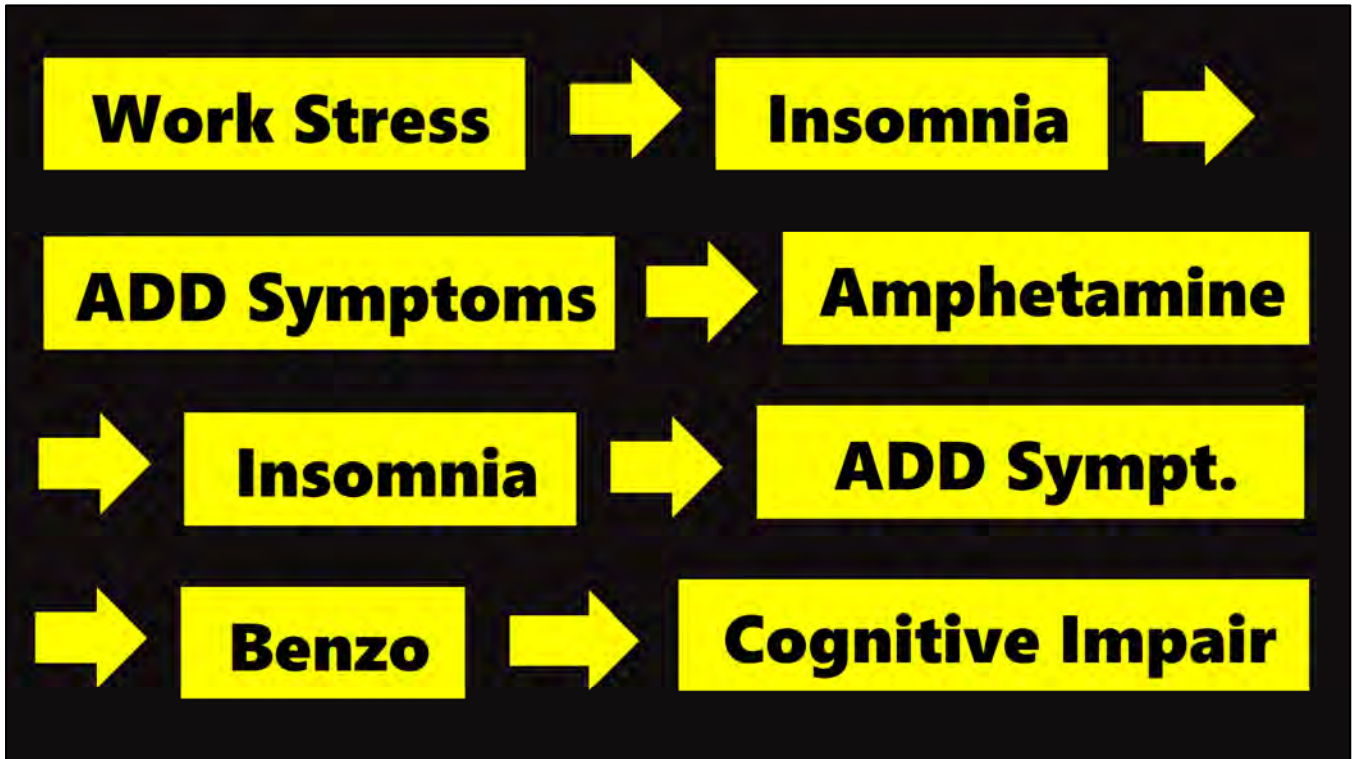
Spence AL et al, Drug Alcohol Depend 2016;166:209-217

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

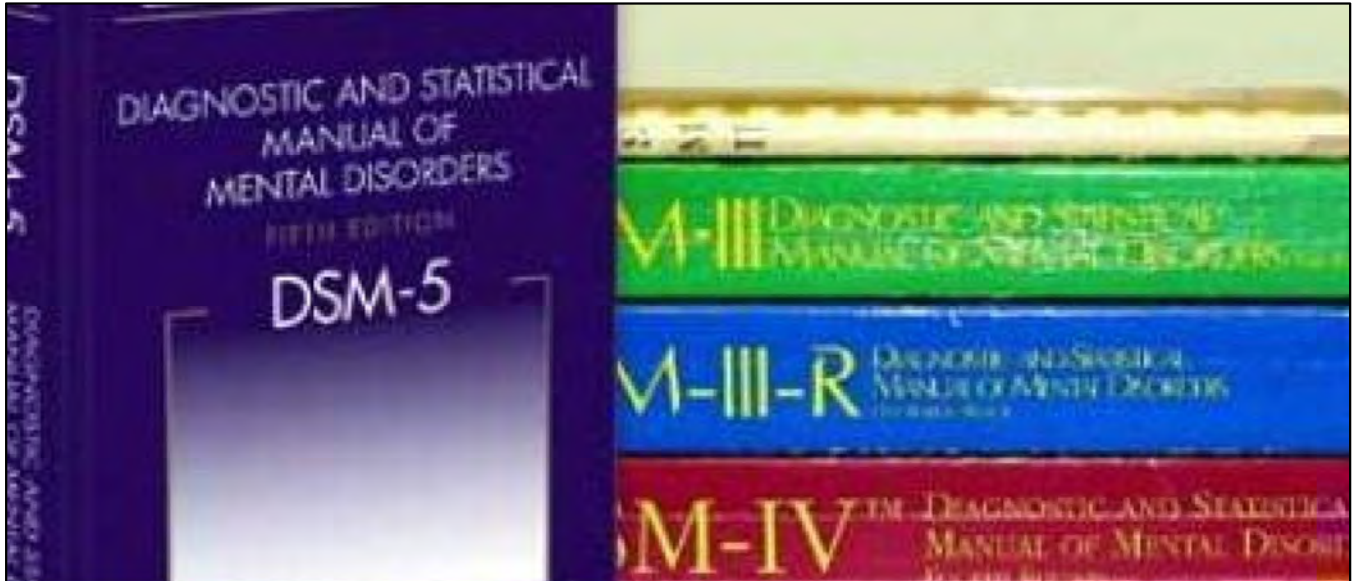


When patients are prescribed stimulants+benzos without a clear diagnosis that indicates them (ie, for “lifestyle” or stress), taper gradually as the use is not indicated and should not be long-term.



Majority (93% to 95%) of “adult onset ADHD” cases are better explained by sleep disorders, substance use disorders, or another psychiatric disorder; also sleep apnea common in ADHD (20-43%).

REFERENCES: Sibley MH et al, Am J Psychiatry. 2018;175(2):140-149; Lopez R et al, Psychiatry Res. 2017;257:238-241, Leow BHW et al, J Atten Disord 2026;30(6).



3. COMPLEX COMORBIDITY: Taper gradually

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

4. Rational use

Stimulant for ADHD

Rare benzo for panic/phobia

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

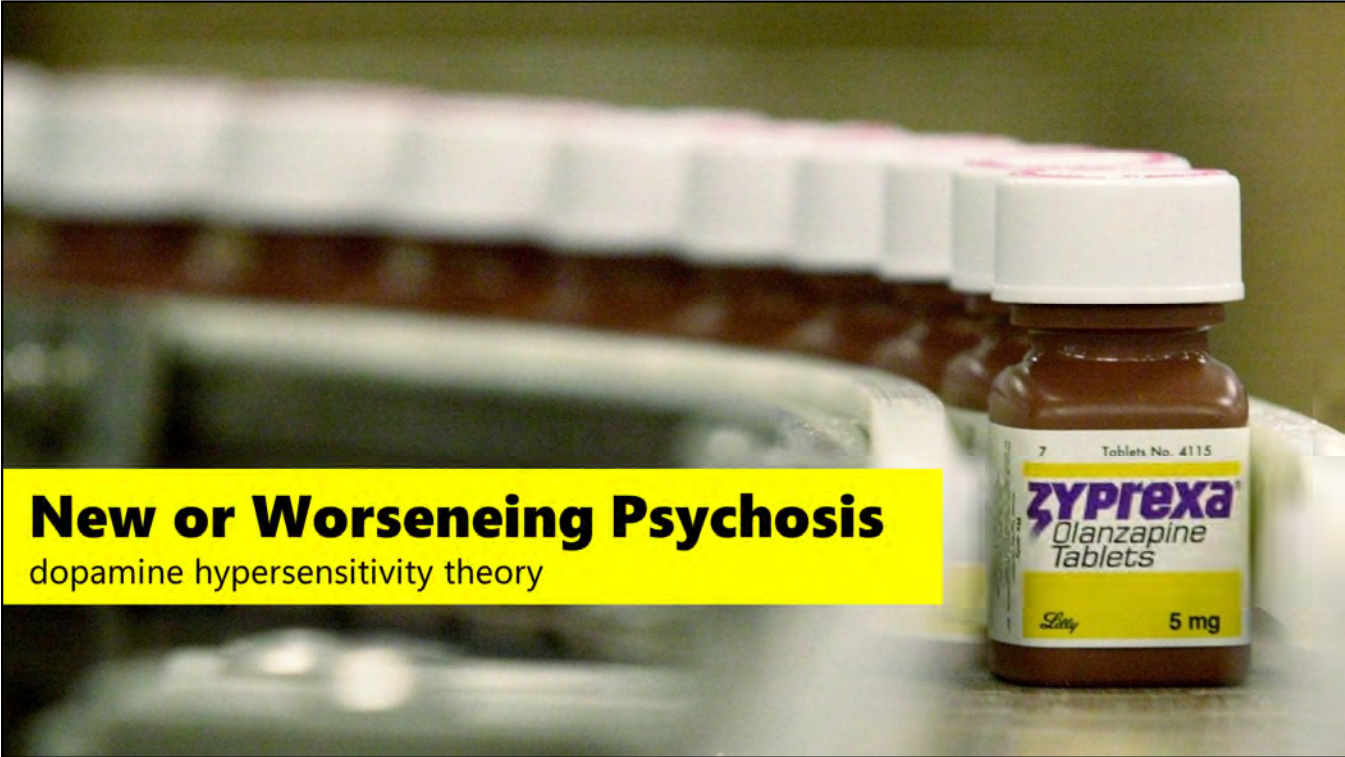


How to Taper

TABLE 45-1. Withdrawal Symptoms by Medication Class

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

Anticholinergics: Cholinergic Rebound



New or Worsening 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

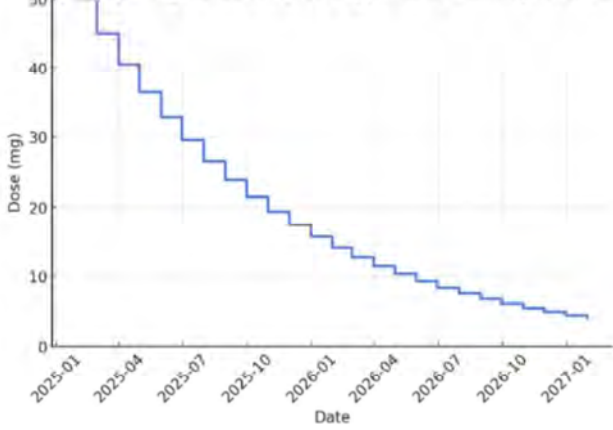
The doses for each step of the final taper are listed in Table 46.1 (eg, citalopram 5 mg, then 3.4 mg). How quickly you go down at each step depends on how sensitive the patient is to withdrawal. Your assessment of their symptoms at baseline and one month later will give you a sense of that. At a minimum, 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

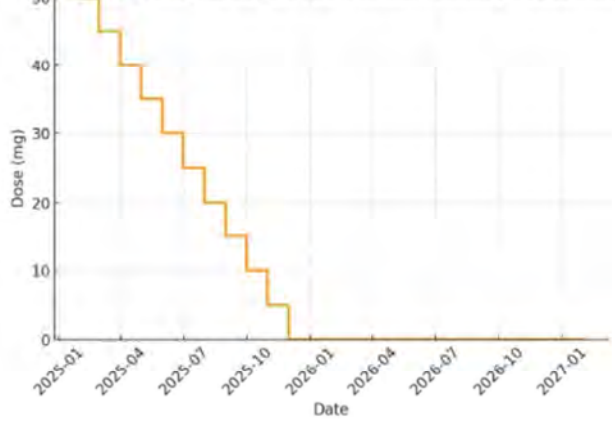
*The minimum daily represents the dose that typically achieves 80% occupancy at the serotonin receptor. It roughly corresponds with the minimum effective dose for depression.

Drug X Tapering Schedule (10% Hyperbolic Monthly Reduction)



Hyperbolic taper

Drug X Tapering Schedule (10% Linear Monthly Reduction)



Linear taper

Home-made emulsions for micro-doses

psych-partners.com/microdosing



Questions?

caiken@thecarlatreport.com

