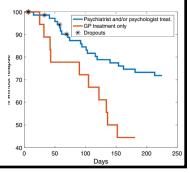
Deciphering Deprescribing: Navigating Reduction Strategies Across Psychiatric Disorders

Part 1: How long do people actually take medication? Why do they stop?



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Learning Objectives

- Describe clinical situations in where discontinuing medication may be an appropriate choice.
- Demonstrate how to talk with patients about the decision to deprescribe medication and the informed consent principles of this conversation.
- Explain the pharmacokinetic principles involved in deprescribing a medication, particularly the concept of hyperbolic tapering.

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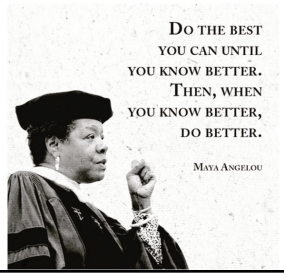
We are good at this…

3

But less skilled at this.

4

Some of this content may challenge what you've been taught.
That's ok.



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How were we taught to answer the big question?
"Do I have to take these for the rest of my life?"

- **Start med**: • Establish tolerability • Establish efficacy
- **Optimization**: • Address side effects • Address residual sx
- **Maintenance**: • 4-9 months? • Forever? • When the pt decides to stop?

C. CONTINUATION PHASE

Continuation phase pharmacotherapy is strongly recommended following successful acute phase antidepressant therapy, with a recommended duration of continuation therapy of approximately 4–9 months (assuming good and consistent control of depression symptoms). The goal of continuation treatment is to prevent relapse (i.e., the re-emergence of significant depressive symptoms or dysfunction) in the vulnerable period immediately following remission (i.e., a complete alleviation of symptoms) (408, 410, 411). The possibility of relapse should be carefully monitored during the continuation phase as this is when risk of relapse is highest (483). Within the first 6 months following recovery from a major depressive episode, relapse of depressive symptoms is common, with the proportion of patients with relapse ranging from 20% of patients in mixed samples (484–487) to as many as 85% of severely depressed inpatients receiving treatment with ECT (234, 488, 489). These studies also show that relapse rates are greater if antidepressant treatment (including ECT) is discontinued or reduced in dose or intensity following recovery (234, 489, 490). There is evidence that patients who do not completely recover during acute treatment have a significantly higher risk of relapse (and a greater need for continuation treatment) than those who have no residual symptoms (227, 491, 492). Similarly, patients

Doctor: You need to take one of this pills everyday for the rest of your life
Him: But there's only 3 pills doctor
Doctor: Exactly

APA (2010) Practice Guideline for the Treatment of Patients With Major Depressive Disorder. Accessed Aug 6 2024 from http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf

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Why not just keep people on meds indefinitely?

- **Long term risks with:**
  - **Antidepressants**: withdrawal symptoms, sexual dysfunction, weight gain, emotional blunting, tardive dysphoria
  - **Antipsychotics**: metabolic issues/weight gain, prolactin elevations, tardive dyskinesia
  - **Anticholinergics**: acceleration of cognitive decline?
  - **Lithium**: renal, thyroid issues, weight gain
  - **Benzodiazepines**: withdrawal symptoms, acceleration of cognitive decline?

Zhang, M. -., Tan, X., Zheng, Y. B., Zeng, N., Li, Z., Horowitz, M. A., Feng, X. Z., Wang, K., Li, Z. Y., Zhu, W. -L., Zhou, X., Xie, P., Zhang, X., Wang, Y., Shi, J., Bao, Y. P., Lu, L., & Li, S. X. (2024). Incidence and risk factors of antidepressant withdrawal symptoms: a meta-analysis and systematic review. *Molecular psychiatry*, 10.1038/s41380-024-02782-6. Advance online publication. https://doi.org/10.1038/s41380-024-02782-6

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Why do people stop meds?

Reason	N	%
Long-term effects	177	74
Adverse effects	175	73
Wanted to know who I am	115	48
Learned about alternative approach	82	34
Felt better	81	34
Drug not useful	70	29
Drug did not work anymore	54	23
Short-term use intended	31	13
Concerned about reproductive health	30	13
Advised to discontinue by prescriber	19	8
Advised to discontinue by health care provider	13	5
No access to medications	10	4
Advised by someone in personal life	10	4
Other	71	29
Item nonresponse	10	—

- Many times, there's more than one reason to consider deprescribing
- Bio-psycho-social factors are all often at play when a deprescribing decision is being made

Ostrow L. et al. *Psychiatric Services*. 2017 December;68:12.

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More reasons why people stop AD's

	Weeks used before discontinuation by patient									
	Total		1–2		3–6		7+			
	%[a]	(s.e.)	%[a]	(s.e.)	%[a]	(s.e.)	%[a]	(s.e.)	$\chi^{2[b]}$	df
Lack of continued need										
Felt better	46.6	(2.8)	51.4	(4.6)	32.8	(5.0)	50.0	(4.1)	7.6*	2
No longer needed[c]	1.8	(0.6)	0.0	(0.0)	2.0	(1.5)	2.7	(1.1)	0.0	1[d]
Total	48.4	(2.8)	51.4	(4.6)	34.9	(5.0)	52.7	(3.9)	7.3*	2
Treatment ineffectiveness										
Medication not working	14.3	(1.2)	13.0	(2.1)	17.3	(3.1)	13.7	(1.9)	1.8	2
Side effects	5.1	(1.0)	2.1	(0.7)	6.5	(3.2)	6.1	(1.3)	7.2*	2
Total	18.5	(1.3)	14.3	(2.2)	21.0	(3.4)	19.0	(1.9)	5.2	2
Predisposing factors[e]										
Fear of dependence	15.3	(1.5)	23.2	(3.7)	12.1	(3.7)	12.5	(1.6)	9.4*	2
Wanted to solve problem on own	7.1	(1.4)	6.8	(1.3)	8.8	(3.9)	6.5	(1.4)	0.6	2
Total	20.0	(2.0)	25.0	(3.5)	20.9	(4.9)	16.9	(2.3)	3.8	2
Enabling factors										
Pressured to quit[f]	4.2	(0.8)	4.3	(0.5)	2.6	(1.6)	4.8	(1.6)	0.8	2
Couldn't afford treatment	1.0	(0.4)	2.5	(1.3)	0.0	(0.0)	0.5	(0.0)	12.1*	1[d]
Total	5.0	(0.9)	6.2	(1.4)	2.6	(1.6)	5.4	(1.6)	1.7	2
Other reasons										
Any other reason	14.2	(1.3)	8.9	(4.0)	26.4	(4.0)	11.9	(1.5)	12.6	2
(n)	(328)		(87)		(67)		(174)			

"It worked, and I don't think I need it"

"It didn't work, or there are too many side effects to want to continue."

"I don't want to be dependent on meds."

"Someone thinks I should stop, or I can't afford them."

Kazdin, A. E., Harris, M. G., Hwang, I., Sampson, N. A., Stein, D. J., Viana, M. C., Vigo, D. V., Wu, C. S., Aguilar-Gaxiola, S., Alonso, J., Benjet, C., Bruffaerts, R., Caldas-Almeida, J. M., Cardoso, G., Cwenkel, E., Chardoul, S., Cia, A., de Jonge, P., Gureje, O., Haro, J. M., ... WHO World Mental Health Survey collaborators (2024). Patterns, predictors, and patient-reported reasons for antidepressant discontinuation in the WHO World Mental Health Surveys. *Psychological medicine*, *54*(1), 57–78. https://doi.org/10.1017/S0033291723003197

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Making Space for Clients to Speak up.

"Research suggests that clients hesitate to assert themselves in clinical encounters out of deference to clinician authority. It is not enough, therefore, to exhort psychiatrists to listen to their clients' preferences when they express them; rather, **it may be necessary to train them to create explicit openings for their experiences clients to articulate their**, such as, for example, explicitly raising medications as a discussion topic."

Morrill, Z. (2019, March 12). How Do Clients Solicit Medication Changes With Psychiatrists? Mad in America. https://www.madinamerica.com/2019/03/clients-solicit-medication-changes-psychiatrists/

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Without Trust Nothing Else Matters

"To pursue the patient's good, the patient must trust the physician (or clinician, or organization) with private information and with his/her body.

Trust in the healer is essential to healing itself.

Trust, at least to some minimal extent, is undoubtedly a prerequisite to seeking care at all."

Expectant or presumptive trust: The predisposition a patient brings to a first encounter

Experiential trust: Develops with knowledge of the one trusted over time.

Identification-based trust: An understanding based on a sense of shared values.

Goold S. D. (2002). Trust, distrust and trustworthiness. *Journal of general internal medicine*, 17(1), 79–81. https://doi.org/10.1046/j.1525-1497.2002.11132.x

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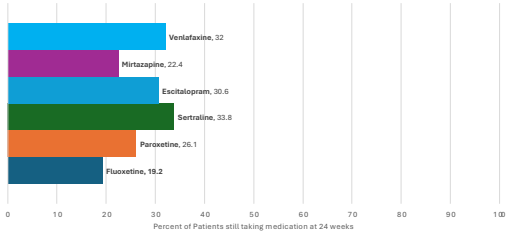
How many of our patients are still taking antidepressants 6 months later?



Jung, W. Y., Jang, S. H., Kim, S. G., Jae, Y. M., Kong, B. G., Kim, H. C., Choe, B. M., Kim, J. G., & Kim, C. R. (2016). Times to Discontinue Antidepressants Over 6 Months in Patients with Major Depressive Disorder. *Psychiatry investigation*, *13*(4), 440–446. https://doi.org/10.4306/pi.2016.13.4.440

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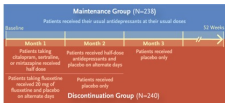
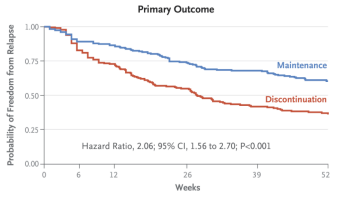
So, what happens when people stop antidepressants?



Secondary Outcomes

	Maintenance (N=238)	Discontinuation (N=240)	Effect Size or Difference (95% CI)
Patient Health Questionnaire-9*	4.2	5.0	0.7 (0.0 to 1.4)
Generalized Anxiety Disorder-7*	3.4	4.1	0.8 (0.1 to 1.4)
Modified Toronto Side Effect Scale	4.0	3.9	0.2 (−0.3 to 0.7)
New or Worsening Symptoms	1.4	1.9	0.5 (0.1 to 0.9)
12-Item Short-Form Health Survey†			
Physical Component	48	49	0.2 (−1.3 to 1.6)
Mental Component	46	44	−2.6 (−4.4 to −0.8)

*Higher scores indicate more severe symptoms.
†Higher scores indicate better quality of life.



Lewis, G., Marston, L., Duffy, L., Freemantle, N., Gilbody, S., Hunter, R., Kendrick, T., Kessler, D., Mangin, D., King, M., Lanham, P., Moore, M., Nazareth, I., Wiles, N., Bacon, F., Bird, M., Brabyn, S., Burns, A., Clarke, C. S., Hunt, A., ... Lewis, G. (2021). Maintenance or Discontinuation of Antidepressants in Primary Care. *The New England journal of medicine*, *385*(14), 1257–1267. https://doi.org/10.1056/NEJMoa2106326

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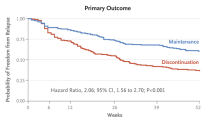
"Staying on the antidepressant does appear to reduce your chances of relapse, somewhat"



Those who stayed on medication were about twice as less likely to have a relapse into depression, compared to those who were tapered off meds.

But there is a cost involved

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How many people get AD-withdrawal symptoms?

- **31%** (95%CI 20-35%) of people d/c AD report w/d symptoms
  - **17%** (95%CI 14-21%) of people d/c a placebo reported w/d symptoms
- **2.8%** of people (1.4-5.7%) report severe w/d symptoms after d/c AD
  - 0.6% (0.2-1.3%) of people d/c a placebo reported w/d symptoms

15%

Henssler, J., Schmidt, Y., Schmidt, U., Schwarzer, G., Bschor, T., & Baethge, C. (2024). Incidence of antidepressant discontinuation symptoms: a systematic review and meta-analysis. *The lancet. Psychiatry*, *11*(7), 526–535. https://doi.org/10.1016/S2215-0366(24)00133-9

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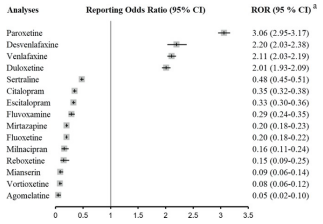
But, the worst offenders have the shortest half lives



Quilichini, J. B., Bevet, A., Garcia, P., Bouguiè, R., Hamard, J., Yrondi, A., & Montastruc, F. (2022). Comparative effects of 15 antidepressants on the risk of withdrawal

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Is it withdrawal, or a return of symptoms?

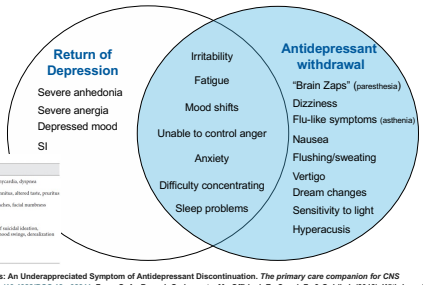

Table 1. Signs and symptoms of withdrawal from SSRI

System involved	Symptoms
General	Flu-like symptoms, fatigue, weakness, tiredness, headache, tachycardia, dyspnea
Balance	Gait instability, ataxia, dizziness, light-headedness, vertigo
Sensory	Paresthesias, electric-shock sensations, myalgias, neuralgias, tinnitus, altered taste, pruritus
Visual	Visual changes, blurred vision
Neuromotor	Tremor, myoclonus, ataxia, muscle rigidity, jerkiness, muscle aches, facial numbness
Vasomotor	Sweating, flushing, chills
Sleep	Insomnia, vivid dreams, nightmares, hypersomnia, lethargy
Gastrointestinal	Nausea, vomiting, diarrhea, anorexia, abdominal pain
Affective	Anxiety, agitation, tension, panic, depression, intensification of suicidal ideation, irritability, impulsiveness, aggression, anger, bouts of crying, mood swings, derealization and depersonalization
Psychotic	Visual and auditory hallucinations
Cognitive	Confusion, decreased concentration, amnesia
Sexual	Genital hypersensitivity, premature ejaculation

Papp, A., & Onton, J. A. (2018). Brain Zaps: An Underappreciated Symptom of Antidepressant Discontinuation. *The primary care companion for CNS disorders*, *20*(6), 18m02311. https://doi.org/10.4088/PCC.18m02311. Fava, G. A., Benasi, G., Lucente, M., Offidani, E., Cosci, F., & Guidi, J. (2018). Withdrawal Symptoms after Serotonin-Noradrenaline Reuptake Inhibitor Discontinuation: Systematic Review. *Psychotherapy and Psychosomatics*, *87*(4), 195–

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Antidepressant withdrawal can be debilitating and increase risk for SI

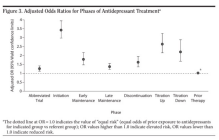
Subjective Experiences of Distress

It took me almost two years to get off Paroxetine and the side effects were horrendous. I even had to quit my job because I felt sick all the time. Even now that I am off of it, I still feel electric shocks in my brain (Pestello & Davis-Berman, 2008).

The difficulty of getting off has been a tough road and taken me years of trying and is something that doctors could be more knowledgeable of and supportive with. (Cartwright et al., 2016).

I forgot to take my Citalopram for two days and woke up one morning with severe dizziness. It was so extreme that I fell over when I tried to get out of bed and I threw up. (Read, Cartwright et al., 2015).

The withdrawal effects if I forget to take my pill are severe shakes, suicidal thoughts, a feeling of too much caffeine in my brain, electric shocks, hallucinations, insane mood swings. ….. kinda stuck on them now coz I'm too scared to come off it. (Gibson, Cartwright, & Read, 2016).



OR 1.61 (p=<.05) suicide risk in the two weeks after suddenly stopping AD, but all adjustment periods confer some risk

Davies, J., & Read, J. (2019). A systematic review into the incidence, severity and duration of antidepressant withdrawal effects: Are guidelines evidence-based? *Addictive behaviors, 97*, 111–121. https://doi.org/10.1016/j.addbeh.2018.08.027
Valuck, R. J., Orton, H. D., & Libby, A. M. (2009). Antidepressant discontinuation and risk of suicide attempt: a retrospective, nested case-control study. *The Journal of clinical psychiatry, 70*(8), 1065–1071. https://doi.org/10.4088/JCP.08m04662

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Let's call it what it is… withdrawal

'The term "discontinuation syndrome" has progressively replaced "withdrawal syndrome" in the antidepressant literature. This shift was heavily supported by the pharmaceutical industry and was aimed to emphasizing that antidepressants do not cause addiction or dependence and symptoms are substantially different from the phenomena that take place with benzodiazepines [2, 78]. The term "discontinuation syndrome" minimizes the vulnerabilities induced by SNRI and should be replaced by "withdrawal syndrome."'

- Fava et al., (2018)

Fava, G. A., Benasi, G., Lucente, M., Offidani, E., Cosci, F., & Guidi, J. (2018). Withdrawal Symptoms after Serotonin-Noradrenaline Reuptake Inhibitor Discontinuation: Systematic Review. *Psychotherapy and Psychosomatics, 87*(4), 195–203. https://doi.org/10.1159/000487506

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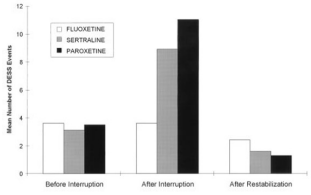
How to measure withdrawal- the Discontinuation Emergent Signs and Symptoms Scale (DESS)



https://hulpgids.nl/assets/files/pdf/DESS.pdf

Fava M. (2006). Prospective studies of adverse events related to antidepressant discontinuation. *The Journal of clinical psychiatry, 67 Suppl 4*, 16–24. Rosenbaum, J. F., Fava, M., Hoog, S. L., Ascroft, R. C., & Krebs, W. B. (1998). Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. *Biological psychiatry, 44*(2), 77–87. https://doi.org/10.1016/s0006-3223(97)00520-7 Fava, G. A., Gatti, A., Belaise, C., Guidi, J., & Offidani, E. (2015). Withdrawal Symptoms after Selective Serotonin Reuptake Inhibitor Discontinuation: A Systematic Review. *Psychotherapy and psychosomatics, 84*(2), 72–81. https://doi.org/10.1159/000370126

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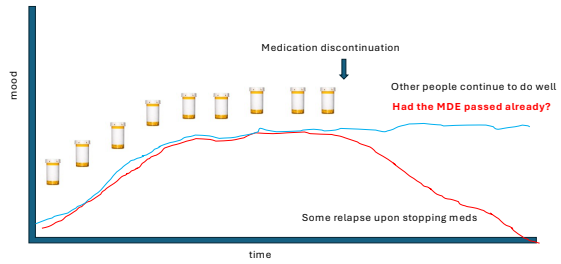
Natural Duration of Acute Depressive Episode is 6-12 months in MDD



Ghaemi SN (2019) *Clinical Psychopharmacology*, Oxford Press. Goodwin FK & Jamison KR (2007) *Manic Depressive Illness*, 2nd ed

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Different Strokes for Different Folks:

Large Variability is Found in Duration of Taper During Deprescribing

- ✓ About one-third (36%) chose to discontinue over a period of more than 6 months
- ✓ Another third (31%) did so in one to six months
- ✓ A third (33%) in less than one month
- ✓ With half of this group (16% of the sample) choosing to do so "cold turkey"

Often, success is achieved only by slowing down the process of deprescribing

Ostrow L, et al. *Psychiatric Services*. December 2017;68:12.

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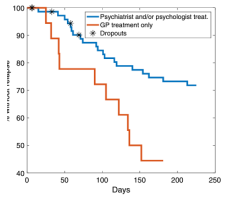
Can we predict who is most likely to relapse with depression?

Unfortunately, not well



*"Residual symptoms increased with discontinuation, **but did not relate to relapse.** Demographic and standard clinical variables **appear to carry little predictive power** and therefore are of limited use for patients and clinicians in guiding clinical decision-making."*

Take home message:
Continue to assess and treat after stopping antidepressants

Berwian, I.M., Wenzel, J.G., Kuehn, L. *et al.* Low predictive power of clinical features for relapse prediction after antidepressant discontinuation in a naturalistic setting. *Sci Rep* 12, 11171 (2022). https://doi.org/10.1038/s41598-022-13893-9

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And what if they do relapse?

- There is a greater possibility of relapse if off the med (compared to staying on it)
  - However, this risk is not massive
- If this happens, restart the medication that worked (ideally, sooner rather than later)
- Underscores the need for early relapse detection (engage the pt in this)

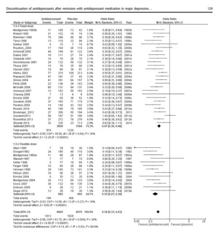

Fig. 5 Meta-analysis of OR for relapse rate by dosing schedule.

Kato, M., Hori, H., Inoue, T., Iga, J., Iwata, M., Inagaki, T., Shinohara, K., Imai, H., Murata, A., Mishima, K., & Tajika, A. (2021). Discontinuation of antidepressants after remission with antidepressant medication in major depressive disorder: a systematic review and meta-analysis. *Molecular psychiatry*, *26*(1), 118–133. https://doi.org/10.1038/s41380-020-0843-0

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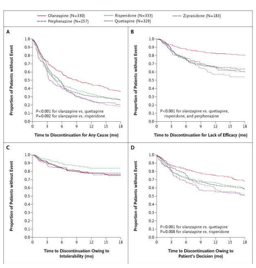
What about other conditions, like schizophrenia?



"Overall, **74 percent of patients discontinued the study medication before 18 months** (1061 of the 1432 patients who received at least one dose): 64 percent of those assigned to olanzapine, 75 percent of those assigned to perphenazine, 82 percent of those assigned to quetiapine, 74 percent of those assigned to risperidone, and 79 percent of those assigned to ziprasidone."

What advice are we giving patients, other than "stay on your meds?"

Lieberman, J. A., Stroup, T. S., McEvoy, J. P., Swartz, M. S., Rosenheck, R. A., Perkins, D. O., Keefe, R. S., Davis, S. M., Davis, C. E., Lebowitz, B. D., Severe, J., Hsiao, J. K., & Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators (2005). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *The New England journal of medicine*, *353*(12), 1209–1223. https://doi.org/10.1056/NEJMoa051688

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Or Bipolar Disorder – a lot of people are stopping meds, largely without guidance

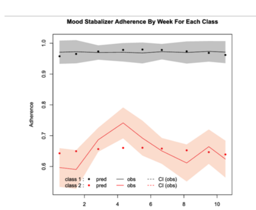

Fig. 1 Mood stabilizer adherence by week for each class. *pred* predicted adherence, *obs* observed adherence, *CI* 91% confidence interval

- "According to the definition of treatment adherence used in the study, combining the DAI, MAQ, and CRS scales, 69.3% of patients (n = 210) were classified as having suboptimal medication adherence." 1
- Sixty-five patients (64%) were noncompliant with their pharmacologic regimen in the month prior to admission as defined by criteria for full compliance and partial or total noncompliance. Noncompliance was significantly associated with greater severity of mania upon admission (p = .02) and treatment with combinations of mood stabilizers (p = .01). 2

1)Montes, J. M., Maurino, J., de Dios, C., & Medina, E. (2013). Suboptimal treatment adherence in bipolar disorder: impact on clinical outcomes and functioning. *Patient preference and adherence*, *7*, 89–94. https://doi.org/10.2147/PPA.S39290
2) Keck, P. E., Jr, McElroy, S. L., Strakowski, S. M., Stanton, S. P., Kizer, D. L., Balistreri, T. M., Bennett, J. A., Tugrul, K. C., & West, S. A. (1996). Factors associated with pharmacologic noncompliance in patients with mania. *The Journal of clinical psychiatry*, *57*(7), 292–297. 3) Bauer, M., Glenn, T., Alda, M. *et al.* Trajectories of adherence to mood stabilizers in patients with bipolar disorder. *Int J Bipolar Disord* 7, 19 (2019). https://doi.org/10.1186/s40345-019-0154-z

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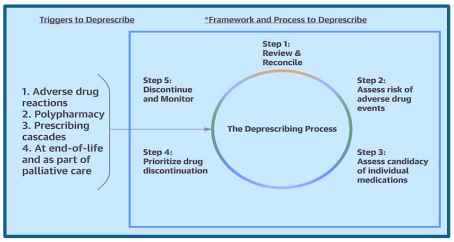
The "Deprescribing Process"
A 5-Step Path to Success, shared with the pt



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Caution for the Deprescribing Clinician
The Road Ahead May be Bumpy, So Bring Your Best A Game to the Table!

Most frequent challenges with deprescribing:

1. Changes in sleep (N=181, 80%),
2. Increased anxiety (76%),
3. Difficulty with emotions (73%)
4. Sadness or tearfulness (70%)
5. Fatigue (69%)
6. Memory and concentration problems (61%)
7. Flu-like symptoms (62%)
8. Diarrhea or constipation (47%)

Asked to rate the overall impact of withdrawal effects on daily activities (from 1, no impact, to 10, severe impact), **54% of respondents reported severe impact** (mean=7.163.1, range 1–10).

Discontinuing psychiatric medication appears to be a complicated and difficult process, although most respondents reported satisfaction with their decision.

Ostrow, L. et al. *Psychiatric Services*. December 2017;68:12.

29

Practical Tips:
7 Steps to Successful Deprescribing

Step 1: Choose the right time

- Avoid times of crisis or acute phase of illness
- Ensure that the treatment alliance is well established
- Use caution when the patient is actively abusing substances

Step 2: Compile a list of all the patient's medications

- Document dose, route, expected duration, and original indication
- Document current therapeutic and adverse effects
- Estimate potential drug-drug interactions and future risk-benefit ratio

Gupta S, et al. *Psychiatric Services*. August 2016;67:8.

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Practical Tips: 7 Steps to Successful Deprescribing

Step 3: Initiate the discussion with the patient

- What is the patient's knowledge and attitudes about the medications?
- What is the patient's perception regarding the benefits and risks of each?
- Explore the meaning of medication(s) to the patient

Step 4: Introduce deprescribing to the patient

- Inform the patient about potential indications for and the process of deprescribing
- Solicit ideas, concerns, and expectations
- Address any anxieties on the part of the prescriber, patient, family, or clinical care team
- Get family and caregiver buy-in

Gupta S, et al. *Psychiatric Services*. August 2016;67:8.

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Practical Tips: 7 Steps to Successful Deprescribing

Step 5: Identify which medication would be most appropriate for a taper

- Collaboratively weigh pros and cons of deprescribing each medication
- Solicit the patient's preferences

Step 6: Develop a plan

- Set a start date and rate of taper
- Is a switch to another medication or formulation indicated?
- Reinforce alternative biopsychosocial strategies for addressing symptoms
- Inform the patient about expected and possible discontinuation effects and their timing
- Agree on a monitoring and follow-up schedule and crisis plan

Gupta S, et al. *Psychiatric Services*. August 2016;67:8.

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Practical Tips: 7 Steps to Successful Deprescribing

Step 7: Monitor and adapt, if necessary

- Adjust rate of taper
- Treat discontinuation syndrome or relapse
- Abort or defer deprescribing

Have a plan but be ***flexible*** and ***agile.***

Gupta S, et al. *Psychiatric Services*. August 2016;67:8.

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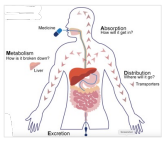
Deciphering Deprescribing: Navigating Reduction Strategies Across Psychiatric Disorders

Part 2: Pharmacokinetics Help To Guide Our Deprescribing Recommendations

Andrew Penn, MS, PMHNP
Clinical Professor
University of California, San Francisco
San Francisco, CA



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Understanding Pharmaco-*Dynamics* and Pharmaco-*Kinetics*

PharmacoDYNAMICS
What the Drug does to the Body

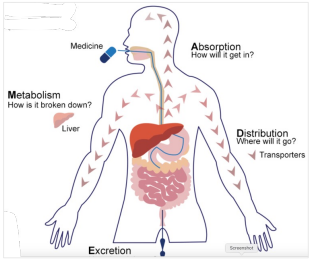
PharmacoKINETICS
What the Body does to the Drug

Pharmacokinetics Basics–Absorption, Distribution, Metabolism and Excretion. April 9, 2011. Accessed April 5, 2023. https://pharmaxchange.info/2011/04/pharmacokinetics-basics-absorption-distribution-metabolism-and-excretion/. Vugmeyster Y, et al. *AAPS J.* 2012;14(4):714-727.

35

ADME – This is *THE* Principle of Pharmacokinetics (PK)

Absorption
⬇
Distribution
⬇
Metabolism
⬇
Elimination



Pharmacokinetics Basics–Absorption, Distribution, Metabolism and Excretion. April 9, 2011. https://pharmaxchange.info/2011/04/pharmacokinetics-basics-absorption-distribution-metabolism-and-excretion/. Accessed July 19, 2019. Vugmeyster Y, et al. *AAPS J.* 2012;14(4):714-727.

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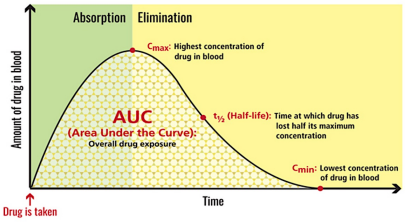
The "Basics" of Pharmacokinetic Profile of Drugs

C_{max}, T_{max}, Half-Life, AUC

Pharmacokinetics



ALL components of a drug's PK Matter

- C_{max}
- C_{min}
- T_{max}
- $T_{½}$ (half-life)
- AUC

Cawello W, et al. *J Clin Pharmacol*. 1997;37(S1):65S-69S. Rowland M, et al. *Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications*. Wolters Kluwer; 2010.

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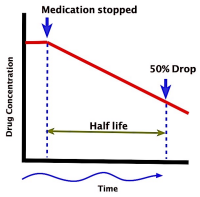
Another Crucial Concept – Half-Life

This is When Half the Drug is Eliminated by the Body



Remember

- Half-life of a drug can vary from individual to another
- Can get longer with age
- Is susceptible to changes with co-administration with other medications that impact its metabolism

Smith DA, et al. *J Med Chem*. 2018;61(10):4273-4282.

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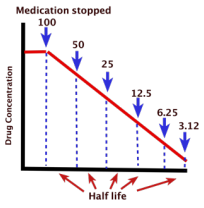
How Fast Does it Drop?

Importance of Knowing Half-Life

Remember

This "Rise" and "Fall" rule applies to both when a drug is being titrated up in an individual, and when it's being discontinued

Some drugs (stimulants) are intended to leave the body each day



Smith DA, et al. *J Med Chem*. 2018;61(10):4273-4282.

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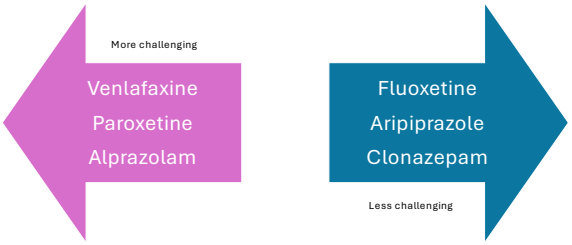
Using Pharmacokinetics, We can Predict What Drugs will Be Easy to Stop and Which will Be Challenging.



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Practical Tips on Deprescribing of Common Psychotropics

- 1) **Necessary?**
  - Ask if the med is still needed
- 2) **Essential?**
  - Ask if behavioral changes could be used in lieu of a med
- 3) **Repeated?**
  - Look for therapeutic redundancies that can be consolidated
- 4) **Short acting?**
  - See if short acting meds can be changed to long acting

- Usually, gradual changes are more tolerable
- Short half-life drugs are more challenging than long-acting

Shelton RC. Steps Following Attainment of Remission: Discontinuation of Antidepressant Therapy. *Primary care companion to the Journal of clinical psychiatry*. 2001;3(4):168–174. Accessed April 5, 2023. https://doi.org/10.4088/pcc.v03n0404. Pottie K, et al. *Canadian Family Physician*. 2018;64:339-351

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When and How to Deprescribe Antidepressants?

- First episode of depression, in remission for a 6-12 months?
- Engaged in behavior changes/therapy?
- Support system and plan in place?

- Sudden discontinuation:
  - *Serotonergic* AD's: Flu-like symptoms, headaches, nausea, dizziness, "brain zaps"
  - Meds with *anticholinergic* side effects cause cholinergic rebound when stopped (restlessness, diarrhea/GI distress/loss of appetite, insomnia)
  - *Noradrenergic* AD's are usually more forgiving (fatigue is common)

Shelton RC. Steps Following Attainment of Remission: Discontinuation of Antidepressant Therapy. *Primary care companion to the Journal of clinical psychiatry*. 2001;3(4):168–174. Accessed April 5, 2023. https://doi.org/10.4088/pcc.v03n0404. Pottie K, et al. *Canadian Family Physician*. 2018;64:339-351

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Table 1 **Approximate half-lives of antidepressants**

Antidepressant	Approximate half-life (days)
citalopram	1.5
escitalopram	1.5
paroxetine	1.0
sertraline	1.1–1.3
fluoxetine	4–16*
fluvoxamine	0.6
vortioxetine	2.4–2.8
agomelatine	0.04–0.08
desvenlafaxine	0.4
duloxetine	0.5
venlafaxine	0.6†
mianserin	0.9–2.5
mirtazepine	0.8–1.6†
reboxetine	0.5
amitriptyline	0.2–1.9
imipramine	0.2–1.3

Short Half Life Predicts Problems

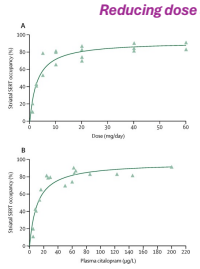
- Longer half life (fluoxetine) meds often need minimal tapering
- Short half life (venlafaxine, paroxetine) need more gradual taper
- Usually the first 50% is unremarkable, but the last 50% may need to be slower

Keks N, et al. Switching and stopping antidepressants. *Aust Prescr.* 2016;39:76-83. Accessed April 5, 2023. https://doi.org/10.18773/austprescr.2016.039.

44

Hyperbolic tapering

Reducing dose at a rate proportionate to receptor occupancy



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.[19] 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

20mg
-10% (-2mg)

18mg
- 10% (1.8mg)

16.2mg
-10% (1.62mg)

14.6mg
-10% (1.46mg)

13.1mg
-10% (1.3mg)

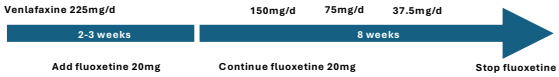
11.8mg…and so on

Horowitz, M. A., & Taylor, D. (2019). Tapering of SSRI treatment to mitigate withdrawal symptoms. *The lancet. Psychiatry*, *6*(6), 538–546.

45

Two Tricks for Tricky Antidepressant Discontinuation

- **Fluoxetine substitution taper:**
  - Take a modest (20mg) dose of fluoxetine for with the other other serotonergic antidepressant for 2-3 weeks
  - After a week, continue fluoxetine while gradually reducing the other med over the course of 4-8 weeks. Then stop fluoxetine. It will fade out of the system.



Shelton RC. Steps Following Attainment of Remission: Discontinuation of Antidepressant Therapy. *Primary care companion to the Journal of Clinical Psychiatry*. 2001;3(4):168–174. Accessed April 5, 2023. https://doi.org/10.4088/pcc.v03n0404

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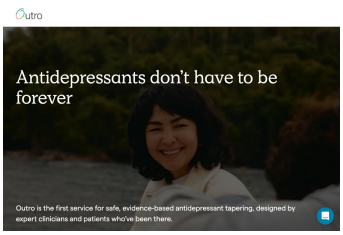
Two Tricks for Tricky Antidepressant Discontinuation

- Liquid microtaper:
  - Continue using, or switch to equivalent dose of available liquid AD's:
    - Fluoxetine
    - Citalopram
    - Escitalopram
    - Paroxetine
  - Reduce by the largest portion that does not result in w/d
  - Or dissolve capsule contents in 100mL orange juice
    - Drink 90mL's, discard rest
    - Reduce by 5-10mL/week until stopped
  - Or use compounding pharmacy or tapering strips

Prabhakar D, et al. Current Psychiatry. 2010;9(11). Groot P (2020) The Pharmaceutical Journal - https://pharmaceutical-journal.com/article/opinion/we-designed-a-new-way-of-tapering-antidepressants-but-why-wont-the-health-authorities-recognise-its-value. TaperingUp.us

47

Telehealth Services offer AD discontiuation



Groot, P. C., & van Os, J. (2020). How user knowledge of psychotropic drug withdrawal resulted in the development of person-specific tapering medication. *Therapeutic advances in psychopharmacology*, *10*, 2045125320932452. https://doi.org/10.1177/2045125320932452
https://www.outro.com

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Deprescribing Antipsychotics

- Usually not appropriate in schizophrenia (usually cross tapered, not stopped)
- Consider in bipolar pts who are on a mood stabilizer
- Consider in MDD once in remission
- Long term use of antipsychotics risks metabolic and movement disorders
- Antipsychotic polypharmacy is often redundant (exceptions: low dose quetiapine for sleep + a full dose antipsychotic; low dose perphenazine + full dose atypical)
- Look for opportunities for consolidation/dose optimization

Pottie K, et al. *Canadian Family Physician*. 2018;64:339-351.

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What if we did short term Tx with SGA's and then withdrew them?

Study: 18 weeks of Brexpiprazole augmentation, then half (N=249) switched to blinded placebo, the other half stays on brex. **Primary outcome measure:** time to relapse.
Finding: both groups were equal (About 20-25% relapsed over 18 weeks), relapse happening about 2 months (63days) later
Clinical implications: Can we do short term SGA augmentation (4-5 months, then stop and monitor for at least 2 mos?)

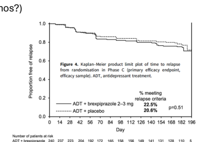
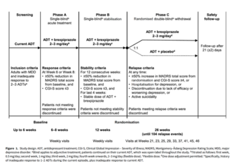


Figure 4. Kaplan–Meier product limit plot of time to relapse from randomisation in Phase C (primary efficacy endpoint, efficacy sample). ADT, antidepressant treatment.

Table 2. Summary of efficacy endpoints in Phase C (efficacy sample)

Endpoint	Treatment group	N	n (%)	Treatment difference: Hazard ratio (95% CI)[a]	p-value
Met relapse criteria	ADT + brexpiprazole	240	54 (22.5)	1.14 (0.78, 1.67)	0.51[b]
	ADT + placebo	248	51 (20.6)		
Met functional relapse criteria	ADT + brexpiprazole	239	81 (33.9)	1.18 (0.86, 1.62)	0.31[b]
	ADT + placebo	243	73 (30.0)		
Met remission criteria at last visit	ADT + brexpiprazole	240	173 (72.1)	–	0.85[c]
	ADT + placebo	247	180 (72.9)		



McIntyre RS, et al. (2024) A double-blind, placebo controlled,randomised withdrawal study of adjunctive brexpiprazole maintenance treatment for major depressive disorder. *Acta Neuropsychiatrica* 1–12. doi: 10.1017/neu.2024.32

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Deprescribing Anti-Cholinergics/Antihistamines

- If you're deprescribing an antipsychotic, don't forget to stop the anticholinergic
  - Benztropine, Trihexyphenidyl
- Some antihistamines (diphenhydramine) are also anticholinergic
- Tricyclic antidepressants and low potency FGA's tend to be anticholinergic
- Anticholinergics can have significant SE:
  - Physical: dry mouth, constipation, blurry vision
  - Cognitive: risks of cognitive impairment (short and long term), risk of delirium
- Tapering is wise to prevent cholinergic rebound

Pottie K, et al. *Canadian Family Physician*. 2018;64:339-351.

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Deprescribing Lithium and Mood Stabilizers

- **In some situations, deprescribing lithium and/or mood stabilizers is appropriate. Great skill is needed to assess if, and when, and how to do so**
- Caution! Ensure ongoing therapy is not indicated. If such therapy is needed, deprescribing is contraindicated
- Substitute treatment with another class of medications is almost always needed in Bipolar Disorder (such as anti-psychotics). In such cases, cross taper gently and slowly
- Finding substitute treatments for anxiety, or another condition the lithium or mood stabilizer is being utilized (consider pharmacological, non-pharmacological, or both options)

Pottie K, et al. *Canadian Family Physician*. 2018;64:339-351.

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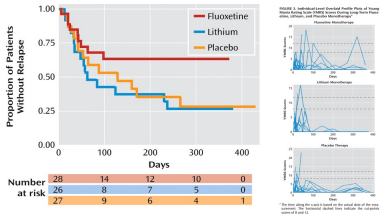
Bipolar disorder – antidepressants – get in, get better, get out?



In bipolar 2 depression,
Antidepressants work, but may cause greater day to day instability

Altshuler, L., Kiriakos, L., Calcagno, J., Goodman, R., Gitlin, M., Frye, M., & Mintz, J. (2001). The impact of antidepressant discontinuation versus antidepressant continuation on 1-year risk for relapse of bipolar depression: a retrospective chart review. *The Journal of clinical psychiatry*, *62*(8), 612–616. https://doi.org/10.4088/jcp.v62n0807 Gitlin M. J. (2018). Antidepressants in bipolar depression: an enduring controversy. *International journal of bipolar disorders*, *6*(1), 25. https://doi.org/10.1186/s40345-018-0133-8 Amsterdam et al (2010) *Am J Psych* 167(7)

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Deprescribing Benzos Begins When You Write Your First Rx

Benzodiazepines = Prednisone?

- Consider NOT starting a benzo (use CBT-I, SSRI instead)
- Start discontinuing benzo before you start prescribing it
  - (set an expectation and schedule for tapering, *like you would with prednisone*)
  - Example Sig:
    - **Lorazepam 0.5mg 1 tab po QAM and 2 tab po QHS.**
    - **After 3 weeks, reduce to 1 tab po BID.**
    - **After 5 weeks, reduce to 1 tab PO QAM.**
    - **After 7 weeks, stop taking med.**
    - **# 42 RF 0.**
- Favor scheduled doses over PRN's

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How to Discontinue a Benzo: *Long-term users*

- Sudden withdrawal (especially daily high doses risks seizures and DT's)
- Consolidate to a single, long-acting drug (diazepam or clonazepam)
  - e.g. 2mg alprazolam = 40mg diazepam
  - Taper no more than 25% per month, slower (10%) if needed in patients who have been using benzos for a long time. *This may take 6-12 months!*
  - Consider adjunctive trazodone, SSRI, β-blocker, melatonin

ASHTON MANUAL
BENZODIAZEPINE EQUIVALENCE TABLE

BENZODIAZEPINE / Z-DRUG	HALF LIFE	APPROX. EQUIVALENT
ALPRAZOLAM (XANAX)	6–12	0.5mg
CHLORDIAZEPOXIDE (LIBRIUM)	5–30	25mg
CLORAZAM (ONFI)	12–60	20mg
CLONAZEPAM (KLONOPIN)	18–50	0.5mg
CLORAZEPATE DIPOTASSIUM (TRANXENE)	36–200	15mg
DIAZEPAM (VALIUM)	20–100	10mg
LORAZEPAM (ATIVAN)	10–20	1mg
TEMAZEPAM (RESTORIL)	8–22	20mg
ZALEPLON (SONATA)	2	20mg
ZOLPIDEM (AMBIEN)	2	20mg
ESZOPICLONE (LUNESTA)	6	3mg

Ashton CH. Benzodiazepines: How They Work and How to Withdraw (aka The Ashton Manual). *Benzo.org.uk*. Revised August, 2002. Accessed April 5, 2023. www.benzo.org.uk/manual/index.htm.

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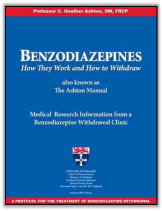
Benzodiazepines: How They Work & How to Withdraw
(aka The Ashton Manual)

Medical Research Information from a Benzodiazepine Withdrawal Clinic

- Ashton Manual Index Page
- Contents Page
- Introduction
- Chapter I: The benzodiazepines: what they do in the body
- Chapter II: How to withdraw from benzodiazepines after long-term use
- Chapter II: Slow withdrawal schedules
- Chapter III: Benzodiazepine withdrawal symptoms, acute and protracted



Ashton CH. Benzodiazepines: How They Work and How to Withdraw (aka The Ashton Manual). *Benzo.org.uk*. Revised August, 2002. Accessed April 5, 2023. www.benzo.org.uk/manual/index.htm.

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MDCalc has a somewhat different range

Benzodiazepine Equivalencies

Medication	Lorazepam Equivalents (mg)
Alprazolam	0.5
Chlordiazepoxide	10–25
Clonazepam	0.25–0.5
Clorazepate	7.5
Diazepam	5
Flurazepam	15
Lorazepam (immediate release)	1
Lorazepam (extended release)	1
Oxazepam	15–30
Temazepam	15
Triazolam	0.25

Source: Park TW. Benzodiazepine use disorder. In: UpToDate. Waltham, MA: Wolters Kluwer; 2023.

ASHTON MANUAL
BENZODIAZEPINE EQUIVALENCE TABLE

BENZODIAZEPINE / Z-DRUG	HALF LIFE	APPROX. EQUIVALENT
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CLONAZEPAM (KLONOPIN)	18–50	0.5mg
CLORAZEPATE DIPOTASSIUM (TRANXENE)	36–200	15mg
DIAZEPAM (VALIUM)	20–100	10mg
LORAZEPAM (ATIVAN)	10–20	1mg
TEMAZEPAM (RESTORIL)	8–22	20mg
ZALEPLON (SONATA)	2	20mg
ZOLPIDEM (AMBIEN)	2	20mg
ESZOPICLONE (LUNESTA)	6	3mg

Take home message:

There may be some individual variance between patients due to differences in drug metabolism, incomplete cross-tolerance, etc.

Assess your patient frequently through this process and adjust as needed.

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Harm Reduction

- Any appropriate reduction is progress
- *Don't let the perfect be the enemy of the good*
- It's more important that *we get there eventually than it is that we get there quickly* (in most cases)
- Be collaborative and creative
- Sometimes, patients find their own tools

Denning P. *Practicing Harm Reduction Psychotherapy.* Guilford; 2000.

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What About Substituting Cannabinoids?

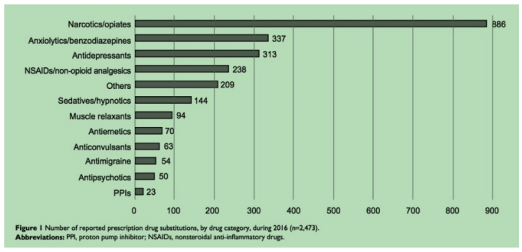
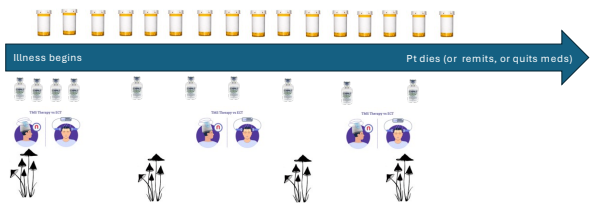


Figure 1 Number of reported prescription drug substitutions, by drug category, during 2016 (n=2,473).
Abbreviations: PPI, proton pump inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs.

Corroon JM, et al. *J Pain Research.* 2017;10:989-998

59

The promise of RAAD's as an alternative to chronic medicatio



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What's not known?

- How does treating depression *episodically* compare to *chronic* treatment?
  - What's the minimum amount of treatment needed to get MDD to stay in remission?
- What is *the minimum duration of treatment with an SGA or lithium* for depression augmentation that provides an enduring effect?

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- Psych meds, especially antidepressants and benzodiazepines can have significant withdrawal effects when stopped
- The decision to stop medications is a complicated one and should be engaged with a process of shared decision making between patient and clinician
- Pharmacokinetics allow us to predict the severity of withdrawal effects. However, withdrawal symptoms and dose have a hyperbolic relationship, requiring a very slow taper of some meds

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Deciphering Deprescribing: Navigating Reduction Strategies Across Psychiatric Disorders

Part 2: Pharmacokinetics Help To Guide Our Deprescribing Recommendations

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Deciphering Deprescribing: Navigating Reduction Strategies Across Psychiatric Disorders

Part 3: Deprescribing Practice Cases

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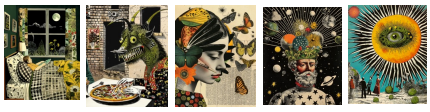

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Somnolent Sam

- 58 year old man with history of depression and chronic early and middle insomnia. He also has low appetite as part of his depression
  - Current meds:
    - Fluoxetine 20mg
    - Trazodone 100mg
    - Doxepin 3mg PRN insomnia
    - Zolpidem 5mg PRN insomnia
  - Past med trials
    - Sertraline, eszopiclone, temazepam, flurazepam, quetiapine, bupropion – none of which worked very well

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Somnolent Sam

- Goal: mirtazapine for depression and sleep
- Process: just add mirtazapine (with fluoxetine and sleeping meds) for now. Some redundancy with trazodone, but no major risks. Encourage holding PRN sleep meds unless needed. Refer to CBT-I if possible.
- 2 months later – mirtazapine at 45mg, depression better addressed. Attempt d/c of fluoxetine (likely no taper needed, because of long half life and low dose, but if w/d sx occur, consider 10mg for a few weeks). Change temazepam to PRN. Attempt holding zolpidem and doxepin.

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Aching Archie

- Archie is a 66 year old man with depression, anxiety, and sciatica pain who comes to you on the following:

- Current meds:
  - Escitalopram 10mg/d
  - Nortriptyline 30mg/d
  - Buspirone 10mg BID
  - Cyclobenzaprine 10mg BID

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Aching Archie

- Plan: reduce BEERS criteria meds, consolidate antidepressant/antinociceptive meds

- Process: either consolidate escitalopram and nortriptyline into a single SNRI (duloxetine, levominalcipran, desvenlafaxine, or venlafaxine OR increase TCA to an antidepressant level (usually 75-150mg and drop the escitalopram. If pain management improves, consider decreasing or stopping the cyclobenzaprine (anticholinergic)

- Given the pt's age, which would you consider first?

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Veronica Venlafaxine

- Veronica is a 46 year old patient who started on venlafaxine 3 years ago during a breakup for depression and anxiety. She is taking 225mg and would like to stop because she feels like her troubles are behind her. Stopped suddenly a few months ago and felt asthenic, nauseated, dizzy and had scalp paresthesias

- Currently taking 225mg venlafaxine ER

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Veronica Venlafaxine

- Reduced dose to 150mg, no problems
- Reduced dose to 75mg, no problems, mood continues euthymic
- Reduced dose to 37.5mg, started to feel "off"

- Returned to 75mg, and added 20mg of fluoxetine for 5 weeks
- Ordered 3x 25mg venlafaxine IR tablets and asked her to quarter them (6.25mg per quarter)
  - Reduce venlafaxine by 1/4 tablet each week (68.75>62.5>56.25>50>etc)
  - Continue the fluoxetine 20mg while reducing venlafaxine over 12 weeks
  - Stop the fluoxetine (or consider a few weeks at 10mg if sensitive)

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Odds and Ends Otto

- Otto is a 38 year old man with history of GAD and MDD who has been stable on the following combination of meds for the last 4 years

- Current meds:
  - Buspirone 5mg TID
  - Gabapentin 300mg BID
  - Sertraline 150mg Qday
  - Hydroxyzine 25mg BID PRN anxiety

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Odds and Ends Otto

- Goal: simplification and consolidation

- Process: Peel back medications one by one to see if they are still needed. Lean hard on the SSRI and try to pull back the other ones.

- Process: think probabilistically about which medication is probably most helpful for both conditions (sertraline). Which is probably least helpful (buspirone, gabapentin, hydroxyzine). Pick one, reduce it slowly, monitor for changes. If needed, consider increasing sertraline to 200mg (optimize).

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GABAbrielle

- 44 year old woman with GAD and possible C-PTSD/borderline PD transferred to my care
- Current meds:
  - CITALOPRAM 50mg QAM
  - BUPROPION 150mg QAM
  - HALOPERIDOL 2-3mg QHS
  - HYDROXYZINE 25mg QID
  - ALPRAZOLAM 3-4mg/d

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Let's practice a benzo conversion

ASHTON MANUAL
BENZODIAZEPINE EQUIVALENCE TABLE

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ALPRAZOLAM (XANAX)	6-12	0.5mg
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- 4mg alprazolam = **80mg diazepam**

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GABAbrielle

- Also smoking 1/8th oz of cannabis per week
- Pt reports that most mornings, she would wake with agitation, tremors, band-like headache, tactile and auditory hallucinations that would abate and hour or two after using cannabis and alprazolam.
- Pt abruptly stopped all medications on impulse and rapidly became psychotic and agitated, and had her first 5150

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The case of GABAbrielle - *my thinking*

- *She's going through benzodiazepine withdrawal (creating a delirium tremens-like presentation), cannabis withdrawal every morning as the alprazolam wears off*
- *Of course, she became agitated when she abruptly stopped all her meds*
- *Acute benzodiazepine withdrawal + labile personality style + possible psychosis = psychiatric emergency*

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GABAbrielle Gets out of the hospital

- She was switched to the following regimen during a 4-day hospitalization. I saw her for the first time 1 day after discharge
- TOPIRAMATE 100mg QAM, 200mg QHS
  - (she had been ramped up on this dose over 3 days)
- HALOPERIDOL 2mg BID
- DIPHENHYDRAMINE 50mg QHS
- HYDROXYZINE 25mg QID
- LORAZEPAM 1mg TID
- OLANZAPINE 5mg Q4 hours PRN agitation

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How Gabi looked out of the hospital

- Pt presents as newly stuporous
  - (this was a somewhat highly functional, educated woman)
- difficulty following conversation
- still with highly labile mood
- Still very anxious (makes sense, given that she'd just had her benzo dose dropped by about 65%)
- Doesn't think the hydroxyzine does anything

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My thinking about GABAbrielle now

- *What a mess, but She'll never have nasal congestion or itching on that much antihistamine!*
- *She's stuporous because of the topirimate*
  - *and to a lesser extent, all the antihistamines*
- *Topirimate is not a mood stabilizer*
- *While she's no longer in acute withdrawal from benzodiazepines, she's still had a big drop in dose.*

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GABAbrielle: What happened next

- I d/c'd topirimate
- I started **valproate** 250 BID
- I changed **olanzapine** to 5mg QID PRN agitation
- I continued **lorazepam** 1mg TID
- I continued **diphenhydramine** 50mg QHS
- I decreased **haloperidol** 2mg QHS
- I discontinued **hydroxyzine**

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The case of Gabi - my thinking

- If her agitation is a bipolar mixed state, let's direct a sedating mood stabilizer/antipsychotic at it, rather than more disinhibiting benzodiazepines
- Valproate has anxiolytic and anti-impulsivity properties in addition to being a mood stabilizer, especially for a mixed state
- The topiramate is causing all negative side effects (stupor) and has no benefit, get rid of it
- If she's taking more olanzapine, she can take a little less haloperidol (we can deal with this one later - prioritizing)
- Eventually, I want to switch her to clonazepam and do an ultra slow taper, but for tonight, let's just keep her out of benzo withdrawals, which are driving her distress and agitation
- Hydroxyzine - if it's not helping, let's get rid of it.

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GABAbrielle : what happened next

- Starts IOP - quit, refused to return
  - It reminded her of Al-anon, which her mother forced her to go to as a teen (trauma reaction)
  - She only wants to see her outpatient therapist (idealizes her) and me
- 5 days after stopping topiramate, cognition is notably improved
- Continues to smoke cannabis, against medical advice. Refuses CD services.
- Continues to have a highly labile mood
- Benzodiazepine withdrawal symptoms seem to have improved
- Ambivalent about medications. Fiancé wants them, she does not.

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GABAbrielle : what happened next

- D/c'd olanzapine and haloperidol
- Started quetiapine 100mg QHS and 50mg TID PRN agitation
- Stopped lorazepam 1mg TID
- Started clonazepam 1mg BID

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GABAbrielle: What happened next

- Fiancé took her to PES, she is admitted on another 5150 and 3 day hospitalization
- Attending doctor kept her on valproate 250mg QID, increased clonazepam to 1mg TID, added zolpidem 10mg QHS and sertraline 50mg QAM
- She gets more hostile while in the hospital, sertraline is discontinued
- Pt fires her outpatient therapist for being in cahoots with me

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GABAbrielle: What happened next

- After 3 days in the hospital, she finally attends IOP
- Less labile and intense. Not hostile. More aware of her reactivity. Sleeping 11 hours per night. Recognizing unresolved grief about her mother's suicide.
- Hospital Discharge meds:
  - Clonazepam 1mg TID
  - Bupropion XL 150mg QAM
  - Valproic acid 500mg BID
  - Trazodone 50mg QHS
- Agrees to IOP, DBT. Agrees to a harm reduction approach to her cannabis use
- Kept her on same meds from discharge

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- Was 2mg clonazepam = **40mg diazepam**
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GABAbrielle: What happened next

- 2 days later, back for IOP, but still wants to leave
- Using less cannabis
- Mood stable, but more depressed.
- Decided to maintain valproate and treat depression with quetiapine
- Restarted quetiapine 50mg QHS
- Ordered a valproic acid level

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GABAbrielle: *my thinking*

- *Keep her engaged in treatment, by hook or by crook!*
- *Quetiapine can be an effective bipolar antidepressant in at the 300mg/d dose*
- *If a mood stabilizer doesn't seem to be working, check that she's getting enough*

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GABAbrielle: what happened next

- VPA comes back at 27 (normal 50-125)
- Admits that she has been taking medication irregularly (waiting until she feels distressed before taking them), but thinks she was using the valproate fairly regularly.
- Increased valproate to 500/1000
- Next VPA level is 90.
- Graduates IOP and starts DBT

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GABAbrielle: what happened next

- Using less cannabis
- Still feeling somewhat depressed
  - Increased bupropion from 150mg to 300mg/d
- She wants to start reducing clonazepam.
- She had already reduced (on her own) to:
  - We decided to drop to 0.5 QAM/0.5mg QPM/1mg QHS
  - We dropped it to 0.5 TID
  - 2 weeks later, we decreased it to 0.5mg BID

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- *We decided to drop to 0.5 QAM/0.5mg QPM/1mg QHS*
  - **(2mg clonaz=40mg diaz)**
- *We dropped it to 0.5 TID*
  - **(1.5mg clonaz = 30mg diaz)**
- *2 weeks later, we decreased it to 0.5mg BID*
  - **(1mg clonaz = 20mg diaz)**

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GABAbrielle: what happened next

- A month later, she continues to feel more stable. In DBT and individual therapy.
- Sleeping well - wants to hold trazodone
- Long conversation about cannabis use. Pt's "all or nothing" dynamic is at play. We decided 12 step groups were too black and white and also too triggering given her childhood with alcoholic mother and al-anon.
- Also acknowledges that she uses cannabis as a "stopgap measure" for her anxiety

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GABAbrielle: 5 months into treatment

- **Original meds**
  - Topirimate 100mg QAM, 200mg QHS
  - Haloperidol 2mg QHS
  - Diphenhydramine 50mg QHS
  - Hydroxyzine 25mg QID
  - Lorazepam 1mg TID
  - Olanzapine 5mg Q4 hours PRN agitation
- **End of this episode meds**
  - Valproic acid 500/1000
  - Quetiapine 50mg QHS
  - Bupropion XL 300mg QAM
  - Occasional Trazodone 50mg HS PRN
  - No benzos!

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Lessons learned

- Use medications that are proven to work for the underlying condition (which in this case was bipolar)
  - VPA (evidence based) vs topirimate (poor evidence)
- Use therapy for things that will respond to it (in this case, crisis needed IOP and hospital level stabilization, her trauma-informed personality structures (borderline PD) needed DBT)
- If you can, check med levels
  - Mood stabilizers, tricyclics
- Cut out medications that don't help
- Push doses until it adds no additional benefit or becomes intolerable

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Lessons learned

- If you're going to use benzos, lean towards longer acting benzodiazepines
  - Clonazepam, lorazepam, diazepam, clorazepate (a pro-drug for desmethyldiazepam, which is the long acting active metabolite of diazepam)
- Avoid redundancies
  - Haloperidol *and* olanzapine?
  - Diphenhydramine *and* hydroxyzine?
- Use side effects to your advantage
- Make sure they are taking them!

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