Best Practices for Tapering off of Benzodiazepines

For those affected by BZWS, deprescription is often a complex process. This analysis and tutorial address only the mechanics and problems of BZD dose reduction. Prior to reading this, you should be familiar with the information contained in Pamphlet 3 – BZRA Discontinuation 1 - Getting Started. Once you are familiar with the best practices for the benzodiazepines tapering process presented in Pamphlet 3, you can complete your understanding of the entire benzodiazepine deprescription process by reading these pamphlets:

Pamphlet 4 - BZRA Discontinuation 2 - Symptomatic Relief
Pamphlet 5 - BZRA Discontinuation 3 - Completion and Repair
Pamphlet 6 - BZRA Discontinuation 4 - It Takes a Team

Note that the term "BZRA" includes both BZDs and Z-drugs.

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1. Benzodiazepine De-prescription is Different

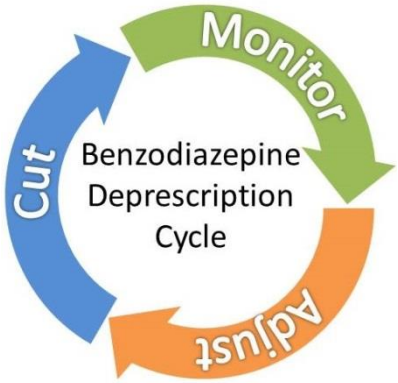

Figure 1: The Benzodiazepine Deprescription Cycle

Unlike the linear method commonly practiced for most other medications, 47% of patients who have use benzodiazepines for more than 4 weeks require a cyclic tapering process.[1] As shown in figure 1, this includes multiple monitoring and adjustment steps in addition to the planned dosage reductions common to other medication classes. The benzodiazepine deprescription cycle has several key attributes.

1.1 "Right sized" dosage changes are required

When tapering a patient off of benzodiazepines, periodic monitoring and adjustments to the amount being cut are usually required. Note that the percentage decreases need to be measured relative to the previous dosage, and not relative to the dosage at the start of the taper. A 10% cut near the end of a benzodiazepine taper may need to be 10 times smaller than a 10% cut at the start of the taper. Unlike the standard medical school deprescription model, this cyclic process is not linear, and yields a deprescription curve similar to what can be seen in figure 2.

At the initiation of a taper, depending on the dosages available for the benzodiazepine being tapered and the desired rate of taper at the time, it may be possible to use lower dosage pills or pill cutting. However, this method may not be possible with those who require a very gradual taper. In such a case, a combination of whole pill(s) and fine or ultrafine tapering may be required. Note that pill cutting is usually too coarse for later reductions.

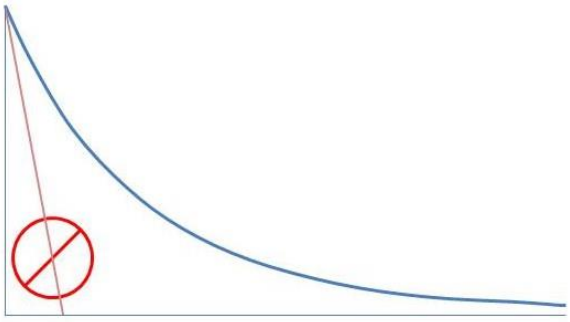

Figure 2: The Benzodiazepine Deprescription Curve: Dose vs Time

1.2 "Therapeutic dose" is not useful during deprescription

The minimal therapeutic dose cannot be used to reliably guide dosage reductions of benzodiazepines. For a surprisingly large percentage of patients, reductions in dosage in the sub-therapeutic range can elicit a significant increase in BZWS symptoms.[2] Even relatively small dose cuts (e.g., 10%) when the current dose is near or below the minimal therapeutic dose may be intolerable or require long recovery times.

1.3 The four parts of a typical BZD taper

For all BZRAs (which includes the Z-drugs), and especially for benzodiazepines, a "typical" taper will consist of up to four parts. For a given patient, it may be possible to skip one or more part.

Precautions for all parts of a taper

1. Although it is difficult to obtain data on drug manufacturers' quality, pharmaceutical manufacturing standards allow BZD strength to vary by +/- 15% between tablets.[3] While this high variability is unlikely within a given lot, it is possible between different lots, and even more likely between different manufacturers. This possible 30% variability is often overlooked, and can be a significant effect for the susceptible patient. The best practice is to stay with the same manufacturer throughout the taper and treat the transition to a new lot number of a given BZD like a cut, allowing equal settling time as provided for a cut. A riskier alternative is to make this transition midway between cuts. Transitioning at the same time as making a cut should be avoided.
2. BZWS patients are often both psychologically and physically compromised, and have difficulty following complex sequential instructions. Given the highly varying nature of benzodiazepine withdrawal symptoms over time for a given patient, it is very important to provide clear, unambiguous instructions.
3. Because it is not safe to alter any kind of modified release tablets, extended-release BZD formulations are inappropriate for tapering.

1.1.1 Part 1: Substitute a long-acting BZD

In general, it has been shown that it is easier to de-prescribe a patient from a benzodiazepine with a longer half-life than from one with a shorter half-life.[4] Problems with inter-dose withdrawal are reduced, and the effects of a given cut are amortized over a longer period of time. Note that this is an optional step, and it can be done at any time. Substitution is based on BZD equivalency tables or calculators. Click HERE for a comparison of benzodiazepine equivalencies using two different calculators.

Precautions for substitution

1. Regardless of the claims of any given source, equivalencies are ranges, and are not exact.[5] These ranges can vary by as much as 2x, which can make substitution very inexact and potentially risky for some benzodiazepines.
2. Depending on the patient and the benzodiazepines involved, substitution can add 1-4 weeks to a taper.
3. Some patients may find substitution intolerable, whether due to the differing phramacokinetics or the equivalency ambiguities of the two benzodiazepines.

1.1.2 Part 2: Coarse taper

This part of deprescription consists of tapering by reducing the number of pills, using pills of reduced dosage, cutting pills, or some combination of these methods. The coarse taper part of deprescription needs to meet all of the requirements for safe BZD deprescription, and this typically limits its applicability to patients who are taking relatively high doses. A coarse taper has the advantages of being more familiar and relatively easy to implement. It can be used until it is no longer viable due to the physical limitations of cutting pills.

For more susceptible individuals, a coarse taper is commonly combined with the fine or ultrafine taper methods to achieve a slower taper rate.

Precautions for coarse taper

1. There is no guarantee of BZD homogeneity within a pill. For most medications, this risk is usually ignored. For the sensitive BZD patient using cut pills, it may be significant.
2. Many BZDs are not scored for cutting, and none are scored for cuts below ½. Patients need to be taught how to minimize the risk of cutting pills, especially at the ¼ pill level.
3. Cuts below ¼ of a pill are not recommended.

1.1.3 Part 3: Fine taper

A slower rate of taper can be achieved by using an oral solution, such as one of the Intensol solutions available for most of the BZDs, along with a finely graduated syringe. Note that this method is only viable until the dose becomes so small that it induces handling problems. See table 1 below for the recommended minimum dosage levels using these solutions.

Precautions for fine taper

1. Intensol solutions are not available for all BZDs prescribed in the US. See table 1 for availability.
2. Since a fine taper uses a solution, it requires multi-step patient instruction and demonstration of competent use of a graduated syringe.
3. A taper using an oral solution requires precision. This is especially true at lower doses, where an imprecise measurement can result in a significant deviation from the desired percentage of dosage reduction.
4. The combination of the methods of a coarse taper with a fine taper may result in a complexity level that is intermittently and unpredictably beyond a given patient's capacity.

1.1.4 Part 4A: Ultrafine taper

For some patients, a very small change in dosage can result in significant exacerbation of withdrawal symptoms. While there is no rigorously controlled research on this topic, substantial anecdotal evidence shows that this may be quite widespread, possibly affecting 10% those undergoing BZD withdrawal.

Additionally, as noted above, the Intensol solutions used in a fine taper are not available for all BZDs. In these cases, the use of a compounded formulation is recommended. Compounded formulations can be made of any BZD, and they allow finer cuts than possible with non-compounded formulations. Diazepam, alprazolam, lorazepam and clonazepam are available as stability-tested compounded formulas (see table 1).

Precautions for ultrafine taper

1. Some BZDs do not have an USP compounding formula.
2. The patient may not have access to a compounding pharmacy.
3. Compounded formulations are usually more expensive. In addition, some insurance companies either do not cover compounded medications or only partially cover their cost.

1.1.5 Part 4B: "Kitchen Chemistry" ultrafine taper

It is important for the clinician to know that their patient may be aware of the availability of many "kitchen chemistry" methods for achieving an ultrafine BZD taper. These include many formulas, videos and other how-to instructional media on the internet.

A. The least risky "kitchen chemistry" method is as follows:

1. Pulverize a whole tablet, or place it a measured (small) amount of water and wait until it disintegrates.
2. Thoroughly mix it in a measured amount of a USP grade suspension vehicle (such as Humco FlavorBlend™ or Specialized Rx SuspendRx™ Anhydrous Base, available online or from a compounding pharmacy).
3. Withdraw a measured amount of the suspended mix and discard it.
4. Consume the remaining suspension.

B. The most readily available "kitchen chemistry" method is as follows:

1. Prepare the tablet as in A.1. above.
2. Mix it for at least 10 seconds with a measured amount of water.
3. While it is being vigorously stirred, withdraw a measured amount of the mixture and discard it. Active agitation during this step is essential.
4. Consume the remaining mixture.

Precautions for "kitchen chemistry" ultrafine taper

1. None of the methods or formulas have undergone systematic review. A sampling shows that they range from risky to harmful. None of these methods are recommended.
2. The method outlined in A. above is the least risky, yet it is imprecise.
3. The biggest problem is that, although BZDs have only a very small solubility in water, most of these methods use water. This leads to unpredictable dispersion of the BZD. Some methods use ethyl alcohol, which has its own set of problems and interferes with BZD action, and should be avoided.

1.4 Table 1: Benzodiazepine Dosages, Solutions and Suspensions [6,7,8]

Benzo-diazepine	Pill Dosages (mg)	Solution			USP Compounded Formulation			
		Type	Strength (mg/ml)	Finest practical cut	Strength (mg/ml)	Finest practical cut	Compound-ing ingredients	Stability
Alprazolam	3*, 2, 1, 0.5, 0.25	Intensol	1	0.02 mg	1	?	?	?
Clonazepam	2, 1, 0.5, 0.25, 0.125	Liquid oral ***	0.1, 0.2, 0.4	0.002 mg	0.1	?	?	?
Diazepam	10, 5, 2	Intensol	5	0.1 mg	1	?	?	?
		Liquid oral	1	0.02 mg		?	?	?
Lorazepam	2, 1, 0.5	Intensol	2	0.04 mg	1	Depends on maximum ingestion of polyethylene glycol?	87% glycerol, 10% polyethylene glycol 400 and 3% propylene glycol	12 mo. @ 4 deg. C [9]
Temazepam	30, 22.5, 15, 7.5	NA			NA			

* Not available in the US *** Available via specialty pharmacies in the UK, but not available in the US.

1.5 Table 2: Benzodiazepine Solubilities [3,4,5,6]

Benzo-diazepine	Solubility (mg/ml)			Stability
	Water	Ethanol	Others	
Alprazolam	0	Yes*	Propylene glycol	?
Clonazepam	0.1	?@90% alcohol/ water	Medium chain triglycerides	?
Diazepam	0.05	62.5	Anhydrous citric acid and polyethylene glycol	?
			Polyethylene glycol and propylene glycol	?
Lorazepam	0.08	14	Polyethylene glycol and propylene glycol	?
Temazepam				

* per label, but no actual solubility listed

2. Sample Tapers

Patient-led benzodiazepine tapers are highly variable. Here are two examples: one a moderate-difficulty taper, and the other a severe case. These are presented to demonstrate the principles used in benzodiazepine tapers, but they also illustrate how pre-set tapering schedules do not meet the needs of the benzodiazepine-dependent patient.

Example 1: Clonazepam, higher dose, moderate case

Patient taking 2 mg clonazepam three times per day for 5 years. Baseline symptoms and severity noted. Patient asks for fast taper, but wants to minimize symptoms.

Day 1: Make first cut, to 1.75 mg tid (three times per day) (12.5%)
Day 2: Check: No significant increase in symptoms. Baseline taper amount established (0.25 mg).
Day 14: Make 2nd cut, to 1.5 mg tid (14.2%) Baseline inter-cut duration set (2 weeks)
Week 4: Significant symptoms noted. Hold for extra week, decrease cuts to 0.125 mg
Week 5: Make 3rd cut, to 1.375 mg tid (8.3%)
Week 7: Make 4th cut, to 1.25 mg tid (9.1%)
…
Week 15: Make 8th cut, to 0.75 mg tid (14.3%)
Week 17: Significant symptoms noted. Hold for extra week, decrease cuts to once per day, 1 week duration
Week 18: Symptoms return to baseline. Make 9th cut, to 0.625 mg AM, 0.75 mg mid-day, and 0.75 mg PM (5.6%)
Week 19: Make 10th cut, to 0.625 mg AM, 0.625 mg mid, and 0.75 mg PM (5.9%)
…
Week 25: Make 16th cut, to 0.375 mg AM, 0.375 mg mid, and 0.5 mg PM (9.1%)
Week 26: Significant symptoms noted. Hold for extra week, increase duration to 2 weeks
Week 27: Symptoms return to baseline. Make 17th cut, to 0.375 / 0.375 / 0.375 mg (9.1%)
Week 29: Make 18th cut, to 0.25 / 0.375 / 0.375 mg (10%)
…
Week 35: Make 21st cut, to 0.125 / 0.25 / 0.25 mg (16.7%)
Week 37: Significant symptoms noted. Hold for extra week, decrease cut to 0.062 mg (1/2 of a 0.125 tablet)
Week 38: Symptoms return to baseline. Make 22nd cut, to 0.125 / 0.188 / 0.25 mg (9.9%)
Week 39: Make 23rd cut, to 0.125 / 0.188 / 0.188 mg (11.1%)
…
Week 45: Make 26th cut, to 0.062 / 0.125 / 0.125 mg (16.5%)
Week 47: Significant symptoms noted. Hold for extra week
Week 49: Symptoms return to baseline. Make 27th cut, to 0.062 / 0.062 / 0.125 mg (20%)
Week 51: Significant symptoms noted. Hold for extra week
Week 52: Symptoms return to baseline. Make 28th cut, to 0.062 / 0.062 / 0.062 mg (25%)
Week 55: Make 29th cut, to 0

Example 2: Alprazolam with transition to diazepam; severe case (but far from the most severe)
Patient taking 1 mg alprazolam twice per day for 2 years. Baseline symptoms and severity noted. Patient asks for gentle taper.

Day 1: Substitute 10 mg diazepam per 1 mg alprazolam; 20 mg once per day.
Day 3: Check for tolerance of substitution. OK.
Day 8: Substitution tolerated. Make first cut, to 18 mg (10%)
Day 10: Check for increase in symptoms. Significant symptoms noted. Adjust cut (up-dose) to 19 mg (5% cut)
Day 12: No significant increase in symptoms (vs baseline) noted. Baseline taper amount established (1 mg)
Day 22: Make second cut, to 18 mg.
Day 24: Significant symptoms noted. Reinstate to 19 mg. Symptoms return to baseline.
Day 28 (Week 4): Make 2nd cut, to 18 mg per day (5.6%)
Day 30: No significant increase in symptoms noted. Baseline inter-cut duration established (3 weeks)
Week 7: Make 3rd cut, to 17 mg (5.9%)
Week 10: Make 4th cut, to 16 mg (6.2%)
…
Week 25: Make 9th cut, to 11 mg (8.3%)
Week 28: Significant symptoms noted. Hold for extra week, decrease cut to 0.5 mg
Week 29: Symptoms return to baseline. Make 10th cut, to 10.5 mg (4.5%), decrease duration to 2 weeks
Week 31: Make 11th cut, to 10 mg (4.8%)
…
Week 49: Make 20th cut, to 5.5 mg (8.3%)
Week 51: Significant symptoms noted. Hold for extra week, decrease cut to 0.3 mg by using Intensol
Week 52: Symptoms return to baseline. Make 21st cut, to 5.2 mg (5.5%)
Week 54: Make 24th cut, to 4.9 mg (5.8%)
…
Week 66: Make 30th cut, to 3.1 mg (8.8%)
Week 68: Significant symptoms noted. Hold for extra week, decrease cut to 0.2 mg
Week 69: Symptoms return to baseline. Make 31st cut, to 2.9 mg (6.5%)
Week 71: Make 32nd cut, to 2.7 mg (6.9%)
…
Week 77: Make 35th cut, to 2.1 mg (8.7%)
Week 79: Significant symptoms noted. Hold for extra week, decrease cut to 0.1 mg
Week 80: Symptoms return to baseline. Make 36th cut, to 2 mg (4.8%)
Week 82: Make 37th cut, to 1.9 mg (5%)
…
Week 98: Make 45th cut, to 1.1 mg (8.3%)
Week 100: Significant symptoms noted. Hold for extra week, decrease cut to 0.05 mg by using Liquid Oral
Week 101: Symptoms return to baseline. Make 46th cut, to 1.05 mg (4.5%)
Week 103: Make 47th cut, to 1 mg (4.8%)
…
Week 123: Make 57th cut, to 0.5 mg (9.1%)
Week 125: Significant symptoms noted. Hold for extra week, decrease cut to 0.03 mg
Week 126: Symptoms return to baseline. Make 58th cut, to 0.47 mg (6%)
Week 128: Make 59th cut, to 0.44 mg (6.4%)
…
Week 138: Make 64th cut, to 0.29 mg (9.4%)
Week 140: Significant symptoms noted. Hold for extra week, decrease cut to 0.02 mg
Week 141: Symptoms to baseline. Make 65th cut, to 0.27 mg (6.9%)
Week 143: Make 66th cut, to 0.25 mg (7.4%)
…
Week 147: Make 68th cut, to 0.21 mg (8.7%)

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Week 151: Significant symptoms noted. Hold for extra week, increase duration to 3 weeks
Week 152: Symptoms to baseline. Make 69th cut, to 0.19 mg (10%)
Week 155: Significant symptoms noted. Hold until symptoms to baseline, make 70th cut, to 0.1 mg (47%)
Week 158+: Hold until symptoms to baseline, make 71st cut, to 0

3. References Used

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[5] Shayanfar A., Fakhree MAA, Acree W, and Jouyban A. Solubility of Lamotrigine, Diazepam, and Clonazepam in Ethanol + Water Mixtures at 298.15 K Journal of Chemical & Engineering Data 2009 54 (3), 1107-1109 DOI: 10.1021/je8007827 ***Abstract***

[6] Nokhodchi A, Shokri J, Barzegar-Jalali M, Ghafourian T. Prediction of benzodiazepines solubility using different cosolvency models. Farmaco. 2002 Jul;57(7):555-7. doi: 10.1016/s0014-827x(02)01247-8. PMID: 12164213. Abstract

[7] Formulations already exist and are available in other countries:

a. Roche manufacturers a 2.5mg/mL formulation that contains API, propylene glycol, glacial acetic acid, saccharin sodium, peach flavor, and brilliant blue.
b. Iraqi pharmacists developed a 2.5mg/mL formulation. Abas et al. (2016). Full Article
c. Two specialty pharmacies in the UK (Thame and Rosemont) manufacture a 0.1mg/mL solution. The Thame formulation uses API, ethanol (96%), and medium chain triglycerides. The Rosemont formulation uses API, ethanol (96%), medium chain triglycerides, saccharin, and levomenthol.

4. Other BZD compounding references

Allen LV, Erickson MA. Stability of acetazolamide, allopurinol, azathioprine, clonazepam, and flucytosine in extemporaneously compounded oral liquids. Am J Health Syst Pharm. 1996b;53(16):1944-49. Abstract

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Wan-Man Ellaria Lee, Ralph A. Lugo, William J. Rusho, Mark MacKay, and John Sweeley. (2004). Chemical stability of extemporaneously prepared lorazepam suspension at two temperatures. The Journal of Pediatric Pharmacology and Therapeutics: Vol. 9, No. 4, pp. 254-258. Abstract

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