The challenges of benzodiazepine tapering and discontinuation and an underutilized interdisciplinary approach

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Abstract

Benzodiazepines can carry significant health risks with long–term use and are especially detrimental to vulnerable populations including seniors and patients with substance use disorders. Unfortunately, it is extremely challenging to deprescribe and discontinue benzodiazepines despite their known public health risk. Due to limited commercially available dosage forms, benzodiazepine dose reductions recommended by current guidelines may not be possible or practical. This may precipitate benzodiazepine withdrawal symptoms such as anxiety, sleep disturbances, and seizures. We propose a collaborative approach with pharmacists, including using compounded suspensions of benzodiazepines, to supplement the existing benzodiazepine deprescribing regimens in clinical practice.

Introduction

Benzodiazepines (BDZs) are approved by Health Canada for short–term management of conditions such as seizures, anxiety, and insomnia.[1,2] However, BDZs are frequently and inappropriately continued long–term due to the development of drug dependence and the overlooked use of non–pharmacological treatments.[3,4] BDZs continue to be widely prescribed long–term despite known detrimental effects on patients and public health. Inappropriate BDZ use costs Canada an estimated $3076 CAD per person per year in hospitalization, emergency department, and outpatient visits.[12]

Deprescribing benzodiazepines is incredibly complicated and challenging.[3,4] This article attempts to raise awareness on how an interdisciplinary collaboration with community pharmacists can help supplement the existing BDZ deprescribing strategies and reduce long–term BDZ usage.

Risk associated with BDZ use

Current literature and guidelines support a strong recommendation to stop long–term use of BDZs.[13-15] Long–term use of BDZs are associated with serious adverse events such as impaired psychomotor and cognitive functioning, dependency, respiratory depression, and mortality.[1-4,6,8,16] Two populations heavily affected by long–term BDZ use are patients with substance use disorder and elderly patients.[2,3,6,7,13,14,17]

On 14 April 2016, the provincial health officer of British Columbia declared a public health emergency due to the rising rates of drug overdoses and deaths. While opioids have been heavily publicized as the culprit for drug overdoses, one third of B.C.'s overdose deaths involve BDZs.[6,7,18] When BDZs are used in conjunction with opioids, they can lead to fatalities as a result of the combined effects on respiratory depression.[4,15,19-22] Methadone maintenance outcomes, such as overdose risk, are negatively affected by concurrent benzodiazepine use.[7,23]

On the other hand, about one in ten Canadian seniors regularly take BDZs for various conditions and are susceptible to many BDZ adverse effects such as psychomotor impairment, cognitive impairment, dementia, delirium, falls, and fractures.[1,2,6,8,10] Compared to young adults, seniors are more sensitive to the depressive effects of the BDZs, partly explained by diminishing metabolic function of the body on the drugs.[4,10] In addition, this particular subpopulation is often taking multiple medications for various medical conditions associated with age thereby increasing the risk of adverse drug interactions.[6]

Challenges with BDZ discontinuation

BDZ withdrawal syndrome includes symptoms such as sleep disturbances, anxiety attacks, palpitations, pain, psychotic reactions, and seizures.[4,15,19-21,24-28] The withdrawal syndrome often mimics the condition that initially led to BDZ prescription, which leads to patients and healthcare providers incorrectly assuming that long-term BDZ treatment is warranted.[3,29] Even in patients that are amicable to BDZ tapering, they perceive withdrawing from BDZ as a difficult, complicated, and highly unpredictable process, with reports suggesting BDZs are harder to discontinue than opioids because of BDZ withdrawal syndrome.[4,28]

Current benzodiazepine gradual dose reduction methods

Method 1: Gradual reduction of current BDZ

Gradual dose reduction is recommended over abrupt discontinuation because it decreases withdrawal symptoms and prevents seizure development.[3,4,27,30] Two Canadian sources of BDZ deprescribing algorithms, the Ontario Pharmacy Education Network (OPEN) and the University of British Columbia's MedStopper, both recommend slowly reducing BDZ doses by 12.5%, 25%, or 50% depending on commercially available dosage forms.[24,31] Regardless of pharmacist experience and quality of equipment, cutting these tablets into ½, ¼, and 1/8 equal sizes is incredibly impractical and inaccurate; even the minute dose differences between the cut tablets can trigger BDZ withdrawal symptoms in sensitive patients.[4,15,19-21,24-26]

Method 2: Implementation of drug–free days

Alternative strategies to reduce the average daily dose, from the OPEN deprescribing algorithm, include using "drug–free days during latter part of tapering" but ultimately this method has the same issue as missing doses.[20,24] Intentionally extending the dosing interval may trigger between–dose withdrawal symptoms.[24,32,33] Skipping doses results in fluctuating drug plasma concentrations and may risk withdrawal symptoms in the patient once the plasma concentration drops below the therapeutic level.[20,21,25]

Method 3: Cross–taper

The most frequently recommended method is to cross–taper to diazepam

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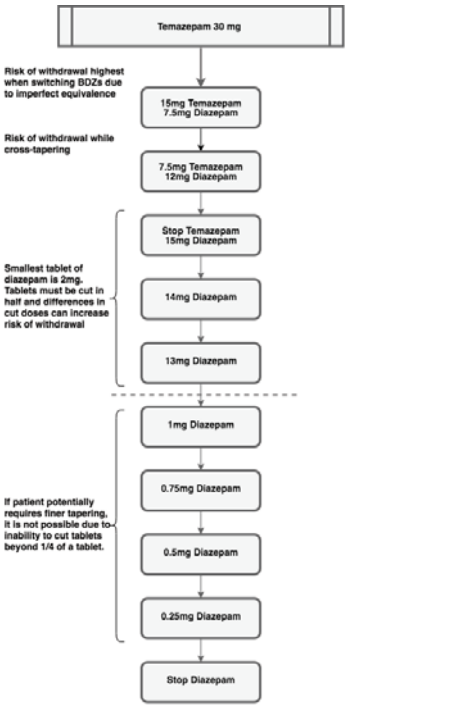

Figure 1: The risks and complexity associated with the Ashton method of BDZ tapering with tablets

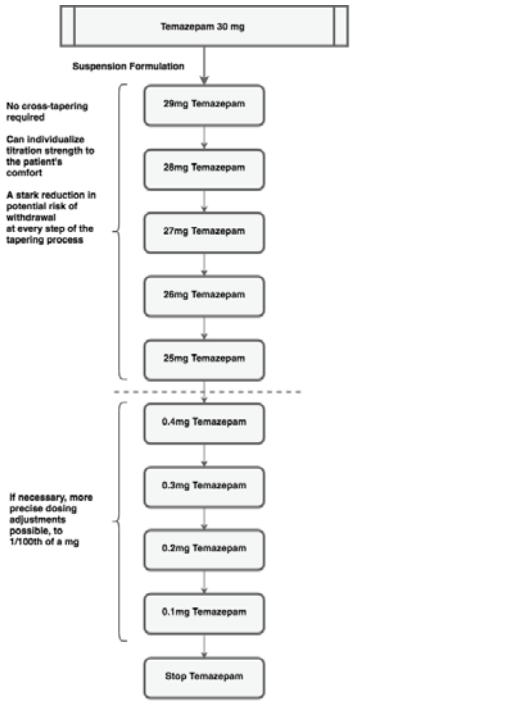

Figure 2: Reduced potential risks and less complexity associated with tapering with a suspension formulation

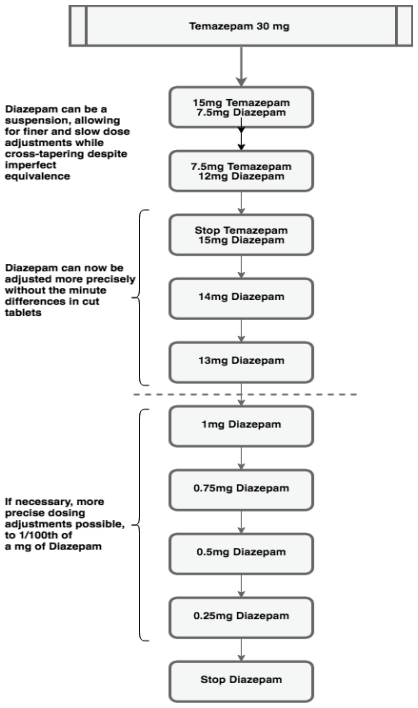

Figure 3: The Ashton Method using a Diazepam suspension

(Valium), a BDZ with a longer half–life.[4,29,30] However, switching one BDZ for another is challenging as BDZ equivalence is poorly described in the literature compared to opioid equipotent dosing.[4,14,34,35] In fact, most benzodiazepine equivalence estimates are based on expert opinions, unreferenced tables in published documents, and clinical experiences.[4,34] Cross–tapering also adds a layer of complexity with confusing calculations for both healthcare providers and patients creating the risk of precipitating withdrawal if conversions are done incorrectly.[10,24,28,36] There is little published evidence stating that switching to a diazepam taper is more effective than other BDZs, can improve outcomes, or reduce incidence of withdrawal symptoms.[10,24,28,36]

Community pharmacists' role in BDZ tapering and discontinuation

Physicians are also often hesitant to deprescribe in general, citing barriers such as lacking the skills and knowledge to deprescribe in a safe and effective manner, fear of withdrawal reactions, and lack of time and support.[37] Physician–pharmacist collaborative settings in primary care can address these barriers and have been shown to decrease inappropriate BDZ use.[38] In addition, community pharmacists are a frequent point of contact for patients and can provide direct patient education to help reduce inappropriate BDZ use, as well as inform the prescriber of any changes or actions required.[39]

In addition to their medication expertise, community pharmacists can compound medications to create dosage forms and strengths that are not commercially available. This underutilized method of using compounded BDZ suspensions can be a very effective strategy in supplementing traditional tapering regimens, allowing for decrements as low as 5% which are useful for patients who are sensitive to dose changes and/or whom are at the end of the tapering regimen and require finer adjustments.[4,16,31,32,40-44]

The Ashton method is shown in Figure 1, with an initial dose of temazepam (Restoril) 30 mg. The Ashton method would involve cross–tapering temazepam to diazepam as per the recommended slow withdrawal schedule.[4] There are several illustrated points in Figure 1 where there is a risk of withdrawal, such as the cross–taper itself, the incongruent doses of diazepam while being tapered, and the final steps of the taper. In Figure 2, we illustrate that using a BDZ suspension does not require cross–tapering, can individualize the titration, and is more precise at smaller doses compared to cut tablets. We chose temazepam as an example, despite its relatively short half–life and consequent higher chance of withdrawal, to emphasize the limitations in the Ashton method. Temazepam cannot be cut in halves or quarters for smaller dose adjustments as temazepam is only commercially available as capsules.

There is also the possibility of combining both methods by switching to diazepam suspension. Note the combined regimen has the advantage of diazepam's longer half–life and lower risk of withdrawal, with the ability to adjust doses more precisely (Figure 3). A temazepam suspension also can potentially be utilized during cross–tapering. This minimizes the risk of withdrawal during cross–tapering and provides flexibility for the patient and physician.

Compounded formulations can carry an increased medication cost for the patient. British Columbia's provincial drug program (PharmaCare) provides some compounded BDZ prescription coverage for BDZ tapering under its exceptional Special Authority criteria for when there is an identified medical need and there are no commercial options available.[45] Community pharmacists can assist with eligibility and coverage issues, reducing barriers to accessing BDZ suspensions for patients and physicians. Specific steps to acquiring special authority for BDZ suspensions are listed in Table 1.

1) Submit written compound request with full explanation: - Indicate that the BDZ compound will be used for tapering - Previous medications and therapies attempted and their outcomes - Starting dose and tapering schedule	**Prescriber Form:** https://www2.gov.bc.ca/assets/gov/health/forms/5479fil.pdf **Pharmacist Form:** https://www2.gov.bc.ca/assets/gov/health/forms/5425fil.pdf
2) Compounding pharmacist submits a completed compound cost sheet and a copy of the prescription	
3) BC Pharmacare will adjudicate on a case-by-base basis, and may provide full, partial, or no coverage	

Table 1 | Steps to obtaining special authority for compounded BDZ from British Columbia Pharmacare

Discussion

BDZs have been a long–established issue and are considered a growing threat to public health.[8,9] Pharmacists are a valuable resource for both patients and prescribers, and meaningful collaboration can be an important factor in improving patient outcomes. Despite highlighting possible benefits of using suspension BDZ over oral formulation, there are limitations such as lack of long–term data on outcomes. The difficulty in discontinuing BDZs and frequency of withdrawals are mostly anecdotal. There is no published evidence stating the superiority of using suspensions over tablets nor does it reduce incidence or severity of withdrawal symptoms. Coverage for BDZ suspensions requires approval and may not be granted for all patients. There is also no optimal speed or duration of gradual dose reduction; however, having the option to adjust doses by 5% is highly beneficial and flexible, and the slower taper may result in greater comfort for patients with less withdrawal incidence.[3,4,28] There is no consensus on a best practice standard for deprescribing BDZs and much more research is needed.[3,10] However, having more options and more allied healthcare practitioners involved in the patient's care can greatly improve the chances of stopping the use of unnecessary BDZs.[3,10]

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