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Corrado Barbui, *Section Editor*

## Discontinuing benzodiazepines: best practices

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In July 2015, the Canadian Agency for Drugs and Technologies in Health (CADTH) released a Rapid Response report summary, with a critical appraisal, on discontinuation strategies for patients with long-term benzodiazepines (BDZ) use. The CADTH document is a review of the literature. It includes studies whose intervention is BDZ discontinuation. Also, clinical guidelines, systematic reviews and meta-analyses are included. What emerges from the CADTH guidelines is that the best strategy remains gradual tapering of BDZ with little evidence for the use of adjunctive medications. The results show that simple interventions such as discontinuation letters from clinicians, self-help information and support in general, added to gradual tapering may be associated with a two- to three-fold higher chance of successful withdrawal, compared with treatment as usual. We suggest possible implications for day-to-day clinical practice.

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In July 2015, the Canadian Agency for Drugs and Technologies in Health (CADTH) released a Rapid Response report summary, with a critical appraisal, on discontinuation strategies for patients with long-term benzodiazepines (BDZ) use (Canadian Agency for Drugs and Technology in Health, 2015). BDZ use is widespread. BDZ are very frequently prescribed (Baldwin *et al.* 2012; Huerta *et al.* 2015) and have been used in anxiety disorders (Berney *et al.* 2008; Offidani *et al.* 2013), although its use declined to the advantage of antidepressants (AD; Berney *et al.* 2008; Katzman *et al.* 2014).

BDZ use is controversial. On the one hand they tend to be quite effective, with a short onset of action and

good tolerability profile (Stahl, 2002). However, there have been increasing concerns over their use, as they can be addictive in the long-term (Lader, 2011) and can cause sedation and drowsiness (Lader, 2011). Also, its use may be problematic in seniors as they can cause increased risk of falls, cognitive decline and delirium (Marra *et al.* 2015). As a consequence, there has been some debate on whether BDZ are dangerous medications, to be used as little as possible (Ashton, 2005), or whether its use has been prematurely discounted (Offidani *et al.* 2013).

In any case, BDZ use can be problematic and can lead to adverse effects. So, long-term use should be carefully evaluated and, if necessary, BDZ dose should be reduced. According to the current evidence, BDZ should be used for a short time (Baldwin *et al.* 2014), or else it may be associated with tolerance or lack of efficacy. This is why a document like the one released by the CADTH, on how to discontinue

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BDZ, can be helpful, as it can offer some guidance on how to safely and effectively stop a potentially problematic medication.

The CADTH document is a review of the literature. It includes studies whose intervention is BDZ discontinuation. Also, clinical guidelines, systematic reviews and meta-analyses are included. The document excludes studies published prior to 2010 and guidelines outside Australia, Canada, the UK and the USA. The population examined is composed by adults in a community setting who took BDZ for longer than 3 months. The aim of this review is to examine the clinical evidence on the BDZ discontinuation strategies. Moreover, another goal is to explore the evidence-based guidelines regarding discontinuation of long-term (i.e. longer than 3 months) BDZ use.

After a comprehensive literature search, the document included three systematic reviews, five randomized controlled trials (RCTs) and three non-RCTs. Mean age for the population ranges from 41 to 79 years. The most common intervention in the included studies is gradual BDZ dose tapering combined with some kind of psychotherapeutic, psycho-educational or psychopharmacological intervention. The comparator is a treatment as usual protocol or a slow tapering without any intervention. The authors of the document did not find any guidelines for BDZ tapering in the literature. The results show that simple interventions such as discontinuation letters from clinicians, self-help information and support in general, are associated with a better chance of successful withdrawal, compared with treatment as usual. The systematic review found that patients who receive simple interventions are twice as likely to completely withdraw from BDZ, compared with controls. If cognitive-behavioural therapy is included as intervention in addition to gradual dose tapering, the percentage of people discontinuing BDZ is between 65 and 85%, compared with dose tapering alone, where the percentage is only 25–54%. Supervised BDZ withdrawal was associated with a higher chance of success. Education interventions were also associated with a higher percentage of discontinuation, 45%, compared with usual care, where only 15% of subjects were able to successfully withdraw from BDZ. With regard to psychopharmacological interventions, it appears that adjuvant medications are not associated with better outcomes. In particular, some of the studies included showed that melatonin was no better than placebo in facilitating BDZ discontinuation (38.1 *v.* 47.7% respectively). Another medication that was included in the comparison was pregabalin, which was associated with successful BDZ withdrawal, with 52% of the subjects achieving BDZ-free status after 12 weeks. However, the study examining this

issue was uncontrolled. Also, hydroxyzine and valerian have been studied. Data show that gradual reduction of BDZ use, in association with hydroxyzine and valerian is associated with abstinence from BDZ in 80.4% of the cases at 6-month follow-up.

What emerges from the CADTH guidelines is that the best strategy remains gradual tapering of BDZ with little evidence for the use of adjunctive medication. Simple interventions may increase the chance of successful withdrawal by two to three times and they may be valuable aids in assisting with BDZ discontinuation.

However, there are still no clear specified guidelines on successful discontinuation. For this reason, the CADTH document is a welcome addition to the literature on BDZ as it gives some guidance on the best strategy to discontinue BDZ. It must be said, though, that the quality of the studies included is not very high and further research is needed. A topic that may also be interesting is what additional psychosocial intervention is most effective in BDZ discontinuation. The studies included in the CADTH review, compared BDZ interventions with treatment as usual. Comparing different types of additional psychosocial interventions may offer some help and can be potentially useful in developing suitable guidelines in BDZ discontinuation. What clinicians should in any case consider, though, is the fact that it is possible to successfully discontinue BDZ, if it is needed.

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#### Conflict of Interest

None.

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