

Prescribing deprescription: a review for a virtuous circle

Prescrever a desprescrição: uma revisão para um círculo virtuoso

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ABSTRACT: Benzodiazepines (BZDs) are generally taken for treating anxiety, insomnia, alcohol abstinence, delirium, and convulsive crises due to their anxiolytic, hypnotic, anticonvulsive, and muscle relaxant activity. These medications must not be taken for more than two to four weeks, but it is common to see patients who take them for even up to 10 years. A review was performed based on NCBI/PubMed (National Center for Biotechnology Information) and SciELO (Scientific Electronic Library Online) databases to become familiar with proposed approaches on deprescriptions of BZDs. The results from the review show how heterogeneous the interventions are regarding the deprescription of BZDs and the need to improve the description to enable adequate replication in clinical practice and research studies.

Keywords: Prescriptions drugs; Deprescriptions; Benzodiazepines.

RESUMO: Os benzodiazepínicos (BZDs) geralmente são utilizados no tratamento de ansiedade, insônia, abstinência alcoólica, delírio e crises convulsivas devido sua atividade ansiolítica, hipnótica, anticonvulsivante e relaxante muscular. Esses medicamentos não devem exceder duas a quatro semanas, mas é comum encontrar pacientes que usam por até 10 anos. Com o objetivo de conhecer as abordagens propostas para desprescrição dos BZDs foi realizada uma revisão embasada nas bases de dados NCBI/PubMed (National Center for Biotechnology Information) e SciELO (Scientific Electronic Library Online). Os resultados da revisão mostram o quanto heterogênea são as intervenções a respeito da desprescrição de BZDs e a necessidade de melhor descrição para permitir uma adequada replicação na prática clínica e em pesquisas.

Descritores: Medicamentos sob prescrição; Desprescrições, Benzodiazepinas.

INTRODUCTION

Benzodiazepines (BZDs) are psychotropic medications acting on the gamma-aminobutyric acid receptor, mediating inhibitory synaptic transmission throughout the central nervous system. They are generally taken for treating anxiety, insomnia, alcohol abstinence, delirium, and convulsive crises due to their anxiolytic, hypnotic, anticonvulsive, and muscle relaxant activity^{1,2}.

BZDs display recommended therapeutic usage for the short-term. Prolonged usage of these substances, even in low dosages, is considered a risk factor causing drowsiness, dizziness, tiredness, mental confusion, headache, anxiety, lethargy, retrograde amnesia, ataxia, postural hypotension, accidents, tolerance, dependence and increased frequent falls. In addition to emotional numbness, ataxia, aggression, nervousness, sedation, and cognitive impairment such as loss of attention, decreased verbal learning and memory,

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and visual and motor difficulties^{2,3}.

These medications must not be taken for more than two to four weeks, but it is common to see patients who take them for even up to 10 years. Around 50% to 70% of patients take BDZs chronically; do not abide by the time as recommended by different publications regarding the safety in taking these medications. Different guidelines have recommended avoiding the use of BDZs as first-choice agents in the treatment of insomnia or even deprescribing them, in case they are currently taken for that purpose^{3,5}.

It is worthwhile to recognize the proposed numerous and heterogeneous approaches in the deprescription of benzodiazepines when considering the current scenario of incorrect usage and the presence of different adverse effects caused by these medications. Deprescription is a collaborative process, in which, contraindicated or possible damaging therapies to patients are modified or discontinued^{4,5}. According to Rodriguez et al. (2018), the responsibility for that activity must be shared among doctors, patients, and if necessary, it must be approached

on different levels of medical care.

MATERIAL AND METHODS

This study is a literature review of articles in June 2019, based on data from NCBI/PubMed (National Center for Biotechnology Information) and SciELO (Scientific Electronic Library Online) using the keywords “prescriptions,” “deprescriptions,” and “benzodiazepines.” The AND Boolean operator was used in each database. There was no limit regarding the publication year of the article or the type of study.

RESULTS

Forty-two articles were found. After reading the title and abstract from these articles, a new selection was performed, excluding articles unrelated to the specific theme. After that, there were ten articles used for preparing this research work (Table 1).

Table 1 - Selected articles

| Author | Title of the article | Journal |
|---------------------------------|-------------------------------------------------------------------------------------------------------------------------|----------------------------|
| Lee et al. ³ | Deprescribing benzodiazepine receptor agonists taken for insomnia: a review and key messages from practice guidelines | Polish Arch Intern Med |
| Brendan et al. ⁸ | Deprescribing Benzodiazepines in Older Patients: Impact of Interventions Targeting Physicians, Pharmacists and Patients | Drugs Aging |
| Limandri ⁵ | Benzodiazepine Use: The Underbelly of the Opioid Epidemic | J Psychosoc Nursing |
| Pottie et al. ¹⁰ | Deprescribing benzodiazepine receptor agonists: evidence-based clinical practice guideline | Can Family Phys |
| Hintze et al. ¹¹ | Hypnotic Discontinuation in Chronic Insomnia | Sleep Med Clin |
| Pruskowski et al. ¹² | Deprescribing and Tapering Benzodiazepines | J Palliative Med |
| Rodriguez et al. ⁴ | Deprescripción de benzodiazepinas y fármacos Z: una responsabilidad compartida | Rev Psiquiatr Salud Mental |
| Reeve et al. ⁶ | A systematic review of interventions to deprescribe benzodiazepines and other hypnotics among older people | Eur J Clin Pharmacol |
| OgBonna et al. ⁹ | Tapering Patients Off of Benzodiazepines | Am Family Phys |
| Pollmann et al. ⁷ | Deprescribing benzodiazepines and Z-drugs in community-dwelling adults: a scoping review | BMC Pharmacol Toxicol |

DISCUSSION

Research studies support BZDs for short-term usage when they are prescribed at low dosages, as they are effective for the treatment of such disorders as panic disorder, generalized, and social anxiety. Even though they initially improve sleep disorders, they reduce the quality of deep sleep and are harmful in their general structure. Physiological as well as psychological dependence develop

in cases of prolonged use, characterized by tolerance, abstinence, and difficulty in reducing or interrupting their use^{5,6}.

The elderly population is among the BZD users who continually take these medications. The majority of these benzodiazepine users are sixty-five or older, taking a defined daily dose (DDD) above the recommended values⁴. According to Rodríguez et al.⁴, it is supposed that the negligence related to pharmacological measures,

such as sleep hygiene and cognitive behavioral therapy is associated with progressive dose reduction in an attempt to suspend the drug that may be related to high DDDs.

Why deprescribe BZDs?

Rodríguez et al.⁴ suggest what the advantages of discontinuing BZDs are, decreased risk of falling, was observed, and improvements of psychomotor and cognitive aspects, such as improved memory and increased alertness levels.

The beneficial effects of BZDs have been noticed to disappear in sleep patterns after tolerance to the medication occurs, as well as the loss of efficacy is admitted as another justification for gradual suspension of this medication. Decreased efficacy is explained by the action mechanism of these medications linked to the benzodiazepine receptor in an "A" type receptor site for γ -aminobutyric acid; however, when taken on a long-term basis, the receptor can change physically and become a less powerful sedative, yet with persistent amnestic effects. Studies have pointed out that decreased therapeutic effect occurs on an average from seven to twenty-eight days. The unfamiliarity of this effect makes these medications be taken inappropriately. That is an extreme concern for the elderly population, due to their potential adverse effects as, for example, falls, fractures, and cognitive problems^{7,8}.

According to Limandri⁵, the most susceptible patients who were prescribed BZDs inappropriately were older women, who, besides all the adverse effects from the medication, the majority of them have some comorbidity that could increase the adverse effects from this medication.

The 2015 Beers Criteria and the Stopp/Start Version 2 Criteria are strong recommendations for avoiding the use of BZDs in the elderly. The first one only recommends taking BZDs for convulsions, sleep disorders in the rapid eye movement phase, alcohol abstinence, and generalized anxiety disorder, under psychiatrist supervision. Whereas, the second one, recommends avoiding the use of BZD for over four weeks and then supports a gradual reduction of the dosage for patients who have been taking it longer to avoid the abstinence syndrome^{8,10}.

Nowadays, we already know that the rapid discontinuation of BZDs is potentially dangerous for those patients who have been taking it daily for over a month. Therefore, gradual reduction plans must be individualized, considering such factors as personality, environmental stressors, and lifestyle. These are the reasons why the patient is taking BZDs. Therefore, it is recommended to explain the medication mechanisms to patients, family members, and caregivers, their adverse effects, benefits, and limitations as to involve them in the treatment. As well as holistically discussing treatment options – combining psychotherapy, cognitive-behavioral, and pharmacological

therapy – to facilitate the prescription and also the deprescription of BZDs^{3,6}.

The more the patients and their families are involved in the treatment, the better the deprescription phase will be. As there had been previous unsuccessful attempts, history of alcoholism and drug use, comorbidities, lack of family support, old age, and an apathetic primary care physician as these are examples of predictive factors associated with degrees of difficulty in this process⁶.

The perceived or actual inaccessibility to alternative treatment modalities may further encourage the renewal of benzodiazepine prescriptions. Patient factors, such as disagreement to cessation, fear of the reoccurrence of symptoms and abstinence, and the inadequacy of alternative treatments also play a role in promoting continued use⁵.

How to deprescribe BZDs?

The purpose of deprescription is essential to reduce the load of medications and their damages while maintaining or improving the quality of life of patients. There are numerous strategies for deprescription in the literature with a significant heterogeneity¹¹.

In the psychological approach, it can be used as a strategy for cognitive-behavioral therapy in different formats, that may be an individual, group, or self-directed, also including, anxiety management, stress management, and psychotherapy^{4,5}.

There have been studies on substituting these drugs for the following medications: buspirone, melatonin, beta-adrenergic receptor antagonists, anticonvulsant drugs (carbamazepine, pregabalin, and valproate), antidepressants (imipramine, paroxetine, and trazodone), the first one has been the most studied. Other drugs are being investigated as ondansetron and progesterone⁷.

The gradual reduction of the dosage as a part of the interruption method was conducted ranging from one to over sixteen weeks, and four weeks was the most common according to the studies. The most common reduction rate among the studies was 25% of the original weekly dosage. Others outlined a slower approach, decreasing the dosage every two to four weeks¹¹.

There were randomized clinical trials involving educational activities and motivational tools on the risks of taking BZDs and the benefits from deprescription. The gradual deprescription process proved to be the most effective in deprescribing BZDs¹².

The success rates for deprescription vary from 57% to 80% as reported from different studies. Articles report significant improvement in cognition, neuropsychological symptoms, balance, and quality of life measurements two to three weeks after medication cessation, including low risk of anxiety and insomnia recurrence^{4,11}.

Some deprescription strategies include (1) informative booklets/folders on damages caused by

chronic use; (2) a self-evaluation questionnaire on damages; (3) inspirational booklets/folders on BZD-use-cessation testimonials; (4) booklets/folders with advice on medical consultation for deprescription; (5) lectures on adverse effects; (6) free sites for aiding in the deprescription process; (7) pharmacological replacement; (8) psychological support, and (9) multidisciplinary interventions, involving doctors, nurses, psychologists, pharmacists, family members, and caregivers¹¹.

Educational activities related to the gradual reduction of the dosage tend to result in a lower degree of discontinuity in taking BZDs when compared to psychological support and pharmacological replacement¹¹.

Patients who are more receptive to deprescription when it is explained clearly to justify that, and then they agree to a deprescription treatment plan, so they know what to expect¹².

CONCLUSION

Chronic and improper use of benzodiazepines continues being a problem for society. This review explicitly expressed how heterogeneous interventions are regarding the deprescription of benzodiazepines and,

mostly, poorly reported. Insufficient details interfere with making clinical practice or research data replication possible. A favorable aspect seen is that the publication frequency remains stable annually, thereby indicating maintained interest in this field, and corroborating with the related risks from taking benzodiazepines. Prolonged use of these substances, even at low dosages, is considered as a risk factor for harmful events to the patient, mainly due to the misuse and the target public taking them.

The correct and carefully prescribed prescription and viewed sensibly gets expected results from these drugs, maintaining the same criterion for withdrawing and deprescribing the same.

The ideal use, respecting the pharmacokinetics and pharmacodynamics of benzodiazepines in the individual, makes it necessary to face risks that misuse imposes as potentially iatrogenic. Thereby, deprescription is as important as the correct prescription. The attention placed on deprescription must be equal or greater than the prescription itself, as the amount of misuse and losses are so high that deprescription becomes part of the treatment. Closing this virtuous circle of careful prescription and responsible deprescription becomes the motto for the care of this public.

Conflict of interest: We hereby declare we have no conflict of interest of any kind: financial, commercial, political, academic, and personal.

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REFERENCES

1. Sgnaolin V, Engroff P, Andrade C, Loureiro F, Nogueira E, Cataldo Neto, A et al. Patterns of chronic benzodiazepine use in the elderly. *Arch Clin Psychiatr*. 2016;43(4):79-82. <http://dx.doi.org/10.1590/0101-60830000000089>.
2. Naloto D, Lopes F, Barberato Filho S, Lopes L, Del Fiol F, Bergamaschi C. Prescrição de benzodiazepínicos para adultos e idosos de um ambulatório de saúde mental. *Ciênc Saúde Coletiva*. 2016;21(4):1267-76. <http://dx.doi.org/10.1590/1413-81232015214.10292015>.
3. Lee J, Farrell B, Holbrook A. De-prescribing benzodiazepine receptor agonists taken for insomnia: a review and key messages from practice guidelines. *Polish Arch Intern Med*. 2019;129(1):43-9. <http://dx.doi.org/10.20452/pamw.4391>.
4. Rodríguez OW, Turiel C, León S, González MJ, Simón M, Fernández Menéndez M. Deprescripción de benzodiazepinas y fármacos Z: una responsabilidad compartida. *Rev Psiquiatr Salud Mental*. 2018;11(3):184-5. <https://doi.org/10.1016/j.rpsm.2018.01.003>.
5. Limandri B. Benzodiazepine use: the underbelly of the opioid epidemic. *J Psychosoc Nursing Mental Health Serv*. 2018;56(6):11-5. <https://doi.org/10.3928/02793695-20180521-03>.
6. Reeve E, Ong M, Wu A, Jansen J, Petrovic M, Gnjjidic D. A systematic review of interventions to deprescribe benzodiazepines and other hypnotics among older people. *Eur J Clin Pharmacol*. 2017;73(8):927-35. <https://doi.org/10.1007/s00228-017-2257-8>
7. Pollmann A, Murphy A, Bergman J, Gardner D. Deprescribing benzodiazepines and Z-drugs in community-dwelling adults: a scoping review. *BMC Pharmacol Toxicol*. 2015;16(1):16-9. <https://doi.org/10.1186/s40360-015-0019-8>.
8. Ng B, Le Couteur D, Hilmer S. Deprescribing benzodiazepines in older patients: impact of interventions targeting physicians, pharmacists, and patients. *Drugs Aging*. 2018;35(6):493-521. <https://doi.org/10.1007/s40266-018-0544-4>
9. Ogbonna C, Lembke A. Tapering patients of benzodiazepines. *Am Fam Phys*. 2017;26(9):606-8. PMID: 29094883.
10. Pottie K, Thompson W, Davies S, Grenier J, Sadowski C, Welch V, et al. Deprescribing benzodiazepine receptor

- agonists Evidence-based clinical practice guideline. *Can Fam Phys.* 2018;64:339-51.
11. Hintze J, Edinger J. Hypnotic discontinuation in chronic insomnia. *Sleep Med Clin.* 2018;13(2):263-70. <http://dx.doi.org/10.1016/j.jsmc.2018.02.008>.
12. Pruskowski J, Rosielle D, Pontiff L, Reitschuler-Cross E. Deprescribing and tapering benzodiazepines #355. *J Palliative Med.* 2018;21(7):1040-1. <http://dx.doi.org/10.1089/jpm.2018.0264>.
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