doi: http://dx.doi.org/10.11606/issn.1679-9836.v102i1(ed.esp.)e-203848 Rev Med (São Paulo). 2023 Jan-Feb;102(1 ed. esp.):e-203848.

Artigo de Revisão

Benzodiazepine dependence and genetic factors: a literature review

Dependência de benzodiazepínicos e fatores genéticos: uma revisão de literatura

Beatriz Milene de Oliveira Camargo[1], Maria Júlia da Gama Fortunato Ziliani[2], Ana Luiza Alvarenga[3], Bianca Calciolari[4], Rafael Shoiti Nagao[5], Luis Felipe Gomes Michelin[6], Aline Alexandrino Antunes[7], Daniel Moreno Garcia[8]

Camargo BMO, Ziliani MJGF, Alvarenca AL, Calciolari B, Nagao RS, Michelin LFG, Antunes AA, Garcia DM. Benzodiazepine dependence and genetic factors: a literature review / *Dependência de benzodiazepínicos e fatores genéticos: uma revisão de literatura.* Rev Med (São Paulo). 2023 Jan-Feb;102(1 ed. esp.):e-203848.

ABSTRACT: Benzodiazepines (BZDs) are psychotropic drugs, central nervous system (CNS) depressants, used worldwide in clinical practice. Its exacerbated consumption and addiction has become a public health issue. The etiology of BZD dependence occurs due to several factors, both genetic and non-genetic. The objective of this review is to compile the genetic factors associated with the dependence mechanisms of BZDs. The genetic mechanisms of BZDs involve interaction with glutamate receptors and GABA modulation, reducing brain activation and memory creation. The BAIAP 3 genotype is the first marker of genetic risk of anxiety and abuse of BZDs. Another mechanism is the polymorphisms of cytochrome P450 monooxygenases enzymes (CYP450). The increase in the chronic use of BZDs has a major impact on public health. Thus, it is essential to analyze the genetic factors that increase dependence, aiming at an individualized therapy and the reduction of this problem.

Keywords: Benzodiazepines; Genetic research; Substance-related disorders.

RESUMO: Os benzodiazepínicos (BZDs) são fármacos psicotrópicos, depressores do sistema nervoso central (SNC), utilizados mundialmente na prática clínica. O seu consumo exacerbado e a dependência se tornaram uma questão de saúde pública. A etiologia da dependência de BZDs ocorre por diversos fatores, genéticos e não genéticos. O objetivo dessa revisão é compilar os fatores genéticos associados aos mecanismos de dependência de BZDs. Os mecanismos genéticos envolvem a interação com receptores de glutamato e modulação do GABA, reduzindo a ativação cerebral e criação de memórias. O genótipo BAIAP 3 é o primeiro marcador de risco genético de ansiedade e abuso de BZDs. Outro mecanismo, ainda, é o polimorfismo das enzimas citocromo P450 monooxigenases (CYP450). O aumento do uso crônico de BZDs tem grande impacto na saúde pública. Dessa forma, faz-se fundamental a análise dos fatores genéticos que aumentam a dependência, objetivando uma terapia individualizada e a redução desta problemática.

Palavras-chave: Benzodiazepinas; Pesquisa em genética; Transtornos relacionados ao uso de substâncias.

XLI COMU 2022 – Congresso Médico Universitário da FMUSP, 15 out. 2022. Monograph Award - 2º colocado.

1. Universidade Anhembi Morumbi, São Paulo, SP. https://orcid.org/0000-0003-3873-3819. E-mail: milenebeatriz1@gmail.com
2. Universidade Anhembi Morumbi, São Paulo, SP. https://orcid.org/0000-0003-0055-0873. E-mail: majufortunato0704@gmail.com
3. Universidade Anhembi Morumbi, São Paulo, SP. https://orcid.org/0000-0001-5455-0882. E-mail: analualvamed@gmail.com
4. Universidade Anhembi Morumbi, São Paulo, SP. https://orcid.org/0000-0002-1415-1315. E-mail: biancacalciolari@gmail.com
5. Universidade Anhembi Morumbi, São Paulo, SP. https://orcid.org/0000-0002-1230-6301. E-mail: rafa11nagao@gmail.com
6. Universidade Anhembi Morumbi, São Paulo, SP. Orientador. https://orcid.org/0000-0002-9741-5442. E-mail: luis.michelin@anhembi.br
7. Universidade Anhembi Morumbi, São Paulo, SP. Orientador. https://orcid.org/0000-0002-8808-9024. E-mail: aline.antunes@anhembi.br
8. Universidade Anhembi Morumbi, São Paulo, SP. Orientador. https://orcid.org/0000-0003-0060-6865. E-mail: dmgarcia@anhembi.br
Endereço para correspondência: Beatriz Milene de Oliveira Camargo. Avenida Jabaquara, 333 - Apto 12 - Chácara Inglesa. São Paulo, SP. CEP: 04045-000. E-mail: milenebeatriz1@gmail.com.

INTRODUCTION

Social dependence is defined as "a maladaptive pattern of substance use leading to significant clinical harm or distress, as evidenced by three or more characteristics that includes tolerance, withdrawal, and abandonment or reduction of important social, occupational, or recreational activities". In this way, drug misuse is defined as the misuse of prescribed substances or the use of these substances for non-therapeutic purposes, by example the ingestion of benzodiazepines with another purpose and the using excessive doses, in addition, the abuse refers to not-prescription drugs, such as ethanol and cocaine[1].

The indiscriminate use of drugs is a global problem: the World Health Organization (WHO) estimated, in 2017, that 42 billion dollars were spent each year on adverse drug-related events. The Third Global Challenge for Patient Safety emerged in this context, inviting countries such as Brazil to collaborate to reduce the aforementioned events by half by 2022[2]. However, there are several difficulties in achieving this goal: there is about one drugstore for every 3,300 inhabitants in Brazil, and we are also in the ranking of the 10 largest drug consumers[3]. There is also a wide range of advertisements for medicines that do not require a prescription, trivializing their consumption. Blay[4], in 2015, estimated that 16.8% of the population of São Paulo had used psychotropic medication at some point in their lives, in which the use of benzodiazepines (BZD) in spite of antidepressants and antipsychotics stands out.

BZDs are drugs of the psychotropic class, which are central nervous system depressants and have anxiolytic, myorelaxant and anticonvulsant properties, characterizing the purpose of their use. These drugs were synthesized for the first time in 1950, in the United States of America, over the years their use has become increasingly high, due to the greater number of diagnoses of psychiatric disorders, in addition to self-medication, inadequate medical prescriptions, media influence, thus defining a public health problem[5].

The etiology of benzodiazepine dependence is complex and multifactorial. Some of the more consolidated risk factors present in the literature are the duration of treatment, doses used, treatment indication, lack of intervention and adequate medical follow-up, abuse of alcohol and other psychoactive substances. There is also some evidence of a higher prevalence in females and advanced age [6].

OBJECTIVE

The main objective of this monograph is to systematically review all the literature available regarding the influence of genetic factors on benzodiazepine dependence.

METHODS

This systematic literature review was created using the Pubmed database using the keywords "benzodiazepine genetic addiction", "benzodiazepine abuse genetic", "benzodiazepine dependence genetics", "benzodiazepine addict pharmacogenetics", "nat2 benzodiazepine", "glutamate benzodiazepine" with the initial number of 2786 articles, that went through a rigorous selection, reaching the final number of 16. The inclusion criteria were: articles in English or Portuguese, consistent with the theme of the article, which describes some genetic mechanism. Exclusion criteria: articles in other languages, which do not cover the topic addressed in the article. In addition to the selected articles, other references were used to complement the text.

RESULTS AND DISCUSSION

The incorrect or improper use of this psychotropic drug is capable of developing levels of dependence associated with both factors of dementia, Alzheimer's and severe falls, especially in the elderly[7]; as to genetic predisposition. The mechanisms of dependence of BZDs have not been completely clarified, and they involve, among others, the interaction with glutamate receptors; responsible for modulating neuronal excitability, release and synaptic plasticity of the central nervous system (CNS). The pathways involved, however, are still being elucidated. The literature shows several evidence of alteration in the expression of metabotropic glutamate receptors (mGluRs), especially in group I[8,9]. Okamoto[10] demonstrates in a study with rats under chronic infusion of diazepam and alprazolam, which develop withdrawal symptoms with administration of flumazenil, the expression of mGluR2 and mGluR3 significantly decreased. This mechanism is similar to changes that occur after repeated exposure to drugs of abuse, resulting from long-term neuroadaptations of the mesocorticolimbic glutamate and dopamine pathways.

In addition to glutamate, BZDs act as GABA ionotropic receptor modulators, that is, they facilitate its inhibitory activity. This receptor has subunits that mediate different behaviors and pharmacological responses[11]. Okamoto[10] quotes an electrophysiological study in which it was possible to verify the relationship between the alpha 1 subunit of the GABA receptor with the development of psychotropic dependence. The effect of this relationship causes a decrease in brain activation; reduction of synaptic plasticity (as well as glutamate), which affects the individual's ability to create new memories and interferes with excitatory synapses, which are necessary for memory[11]. Although still uncertain, this is one of the hypotheses that support the association of prolonged use of BZDs with an increased risk of Alzheimer's disease and dementia. Another plausible assumption would be the

limitation of the cognitive reserve capacity induced by the irregular use of psychotropic drugs, which may reduce the ability to deal with brain injuries at an early stage[12]. In any case, the collections are sufficient to avoid long-term indiscriminate use and prescriptions that are not justified should be considered public health problems[12].

Angiogenesis inhibitor-associated protein 3 is part of the MUNC13 protein family, which is important in the synaptic regulation of neurotransmitter exocytosis and fundamental in the junction of synaptic vesicle membranes that have neurotransmitters such as GABA, highly expressed in brain areas. These regions correspond to the amygdala, hypothalamus and periaqueductal gray matter, which are responsible for regulating autonomic functions, stimulus and fear processing, that is, strongly related to aspects of anxiety[13].

The cellular function of BAIAP3 has not yet been fully identified, but in 2013, Wojcik[14] carried out an experimental study to analyze mice and their genetic variations that influence the risk for the development of tolerance, dependence and withdrawal from drugs such as benzodiazepines. This scientific project shows that female mice carrying the BAIAP3 homozygous genotypes are more likely to have criteria for the diagnosis of anxiety, while male mice carrying the same genotype are more likely to have criteria for benzodiazepine use disorders.

In order to study the functioning of BAIAP3, the analysis of the behavior of mice together with the phenotype-based genetic association (PGAS) of the human BAIAP3 gene was performed. Thus, it was evidenced that BAIAP3 is the first genetic risk marker for anxiety and benzodiazepine abuse in mice and humans, in the tested drugs - short-acting midazolam and long-acting diazepam[14].

Another mechanism of genetic predisposition can be expressed in polymorphisms in the family of cytochrome P450 monooxygenases (CYP450) enzymes, which act in modulating the metabolism of approximately 70% of drugs[15]. Thus, it is known that CYP450 is constituted in humans by a family of 57 genes[16] , with CYP1, CYP2 and CYP3 being the most important families for hepatic drug metabolism, including BZDs[17], since the CYP3A4, CYP2D6, CYP1A2, CYP2C9 and CYP2C19 subfamilies are responsible for metabolizing most antidepressants and BZDs. Thus, CYP metabolism can be slow, intermediate, fast or ultra-fast, due to polymorphisms[16].

Regarding the CYP450 subfamilies, it is known that CYP3A4, which is mainly expressed in the liver (95%) is qualitatively the most important in adults in terms of drug metabolism[15], of this for example, clonazepam metabolism can be mentioned, whose biotransformation is mainly mediated by CYP3A4 and N-acetyltransferase-2 (NAT2). In addition, a small part of CYP3A4 is expressed in the small intestine, which enables pre-systemic and systemic contribution in approximately 30% of drugs[15].

Physiologically, women may have greater CYP3A4 activity[16]. In addition, multiple pharmacokinetic interactions arising from the broad spectrum of substrates were observed. Such interactions can result in clinical complications, such as: increased focus, reduced creatinine clearance, increased neurotoxicity in women with the CYP3A4*22 polymorphism. It was observed that the genetic variant CYP3A4*22 is related to the reduction of messenger RNA and, consequently, there is a decrease in the enzymatic activity of CYP3A4[15].

CYP450 is involved in hydroxylation, termination of steroid hormone activity and bile acid metabolism pathways and activation of various carcinogens. So, it is believed that oral contraceptives that have ethinylestradiol, a similar to endogenous estrogen, inactivate CYP3A4, as they are mainly metabolized by it, as well as 2-hydroxy ethinyl estradiol and at least three catecholamine metabolites that are dopamine, epinephrine and norepinephrine[18].

NAT2 is a gene with phenotypic variations, which divides the population into slow and fast acetylators. The expression of CYP3A4 and the NAT2 acetylator phenotype, analyzed in a prospective trial, can identify which patients are most at risk of having an adverse reaction, as well as improve personalized therapy with benzodiazepines and their withdrawal [19]. With advancing age, an increase in the number of drugs, therapeutic failures and adverse reactions can be observed[20]. Consequently, it would be ideal to know the genetics of CYP individually so that there is a prediction and reduction of the prevalence of therapeutic failures and adverse reactions, constituting a personalized medicine in elderly patients[21].

CONCLUSION

BZDs are classified as one of the most used types of psychotropic drugs worldwide in clinical practice, including in Brazil[5]. The increase in the indiscriminate use of these drugs for recreational purposes and unnecessary medical prescriptions, especially among university students, culminates in a greater number of individuals who develop tolerance and dependence due to chronic use[22], in addition to triggering potentiated side effects. The population's lack of knowledge regarding these side effects, together with the dependence that is created, have a great impact on public health, and it is extremely important to analyze the prevalence of BZD abuse in the academic population, as well as understanding the associated genetic factors, with the final aim to consolidate the results and data generated, and ensure a review that makes it possible to effectively reverse this situation, through educational actions for the community, in order to develop the critical sense of individuals and health professionals.

Thus, it is concluded that there is a correlation between genetic factors and dependence on BZDs, through several mechanisms already reported in literature. Among them, the alteration of the expression of glutamate and GABA

receptors; the homozygosity of the BAIAP3 genotype; the CYP enzyme family polymorphism and NAT2 acetylator phenotype. Therefore, it is necessary further elucidation of the mechanisms involved for possible individualized clinical management of treatment with BZDs; aiming at a lower dependency rate and better therapeutic choices.

Participação dos autores: *Beatriz Milene de Oliveira Camargo:* Revisão de literatura, Elaboração do artigo, Elaboração de documentos. *Maria Júlia Da Gama Fortunato Ziliani:* Revisão de literatura, Elaboração do artigo. *Ana Luiza Alvarenga*: Revisão de literatura, Elaboração do artigo. *Bianca Calciolari*: Revisão de literatura, Elaboração do artigo. *Rafael Shoiti Nagao:* Revisão de literatura, Elaboração do artigo. *Luis Felipe Gomes Michelin:* Orientação. *Aline Alexandrino Antunes:* Orientação. *Daniel Moreno Garcia:* Orientação.

REFERÊNCIAS

1. Schukit MA, Helzer JE, Cottler LB, Crowley T, Nathan PE, Woody GE. Transtornos relacionados a substâncias. In: American Psychiatric Association. Manual diagnóstico e estatístico de transtornos mentais: DSM - IV. Porto Alegre: Artes Médicas; 2014. p.191-295.
2. Agência Nacional de Vigilância Sanitária (ANVISA). Comunicado GGMON 003/2021. Notificação de eventos adversos a medicamentos [citado 04 abr. 2021]. Disponível em: https://www.gov.br/anvisa/pt-br/assuntos/fiscalizacao-e-monitoramento/farmacovigilancia/comunicados/comunicado-ggmon-003-2021/view
3. Brasil. Ministério da Saúde. Conselho Nacional de Saúde. Consumo de medicamentos: um autocuidado perigoso [citado em 2005]. Disponível em: http://www.conselho.saude.gov.br/ultimas_noticias/2005/medicamentos.htm
4. Blay SL, Fillenbaum GG, Pelusco ET. Factors associated with antidepressant, anxiolytic, and other psychiatric symptoms in the city of São Paulo, in Brazil. Int Clin Psychopharmacol. 2015;29(3):157-165. doi: https://doi.org/10.1097%2FYIC.0000000000000008
5. Mendes KCC, Barcelos EM. O uso prolongado de benzodiazepínicos: uma revisão de literatura. Pompéu: Institutional Repository of the Federal University of Minas Gerais; 2013. Disponível em: http://hdl.handle.net/1843/BUBD-9EGHKM
6. Konopka A, Mak M, Grzywacz A, Murawiec S, Samochowiec J. Genetic and psychosocial factors for benzodiazepine addiction. An analysis based on the results of the authors' own research conducted in a group of benzodiazepine addicted and non-addicted individuals. Postepy Hig Med Dosw (Online). 2017;13(1):205-213. doi: https://doi.org/10.5604/01.3001.0010.3805.
7. Seppala LJ, Wermelink AMAT, de Vries M, Ploegmakers KJ, van de Glind EMM, Daams JG, et al. Fall-risk-increasing drugs: a systematic review and meta-analysis: II. Psychotropics. J Am Med Dir Assoc. 2018;19(4):371.e11-371.e17. doi: https://doi.org/10.1016/j.jamda.2017.12.098
8. Mortensen M, Suzdak PD, Thomsen C. The effect of lorazepam tolerance and withdrawal on metabotropic glutamate receptor function. J Pharmacol Exp Ther. 1995;274(1):155-63. Disponível em: https://pubmed.ncbi.nlm.nih.gov/7616393/
9. Suzuki T, Shimizu N, Tsuda M, Soma M, Misawa M. Role of metabotropic glutamate receptors in the hypersusceptibility to pentylenetetrazole-induced seizure during diazepam withdrawal. Eur J Pharmacol. 1999;369(2):163-8. doi: https://doi.org/10.1016/s0014-2999(99)00082-5
10. Okamoto R, Itoh Y, Murata Y, Kobayashi D, Hosoi M, Mine K. Reduction of group II metabotropic glutamate receptors during development of benzodiazepine dependence. Pharmacology. 2013;91(3-4):145-152. doi: https://doi.org/10.1159/000346440
11. Ettcheto M, Olloquequi J, Sánchez-López E, Busquets O, Cano A, Manzine PR, et al. Benzodiazepines and related drugs as a risk factor in Alzheimer's disease dementia. Front Aging Neurosci. 2020;11:344. doi: https://doi.org/10.3389/fnagi.2019.00344
12. Billioti de Gage S, Moride Y, Ducruet T, Kurth T, Verdoux H, Tournier M, et al. Benzodiazepine use and risk of Alzheimer's disease: case-control study. BMJ. 2014;349:g5205. doi: https://doi.org/10.1136/bmj.g5205
13. Zhang X, Jiang S, Mitok KA, Li L, Attie AD, Martin TFJ. BAIAP3, a C2 domain-containing Munc13 protein, controls the fate of dense-core vesicles in neuroendocrine cells. J Cell Biol. 2017;216(7):2151-2166. doi: https://doi.org/10.1083/jcb.201702099
14. Wojcik SM, Tantra M, Stepniak B, Man KN, Müller-Ribbe K, Begemann M, et al. Genetic markers of a Munc13 protein family member, BAIAP3, are gender specifically associated with anxiety and benzodiazepine abuse in mice and humans. Mol Med. 2013;19(1):135-48. doi: https://doi.org/10.2119/molmed.2013.00033
15. Werk AN, Cascorbi I. Functional gene variants of CYP3A4. Clin Pharmacol Ther. 2014;96(3):340-8. doi: https://doi.org/10.1038/clpt.2014.129
16. Tiwari AK, Souza RP, Müller DJ. Pharmacogenetics of anxiolytic drugs. J Neural Transm (Vienna). 2009;116(6):667-677. doi: https://doi.org/10.1007/s00702-009-0229-6
17. Tornio A, Backman JT. Cytochrome P450 in pharmacogenetics: an update. Adv Pharmacol. 2018;83:3-32. doi: https://doi.org/10.1016/bs.apha.2018.04.007
18. Zhou SF. Drugs behave as substrates, inhibitors and inducers of human cytochrome P450 3A4. Curr Drug Metab. 2008;9(4):310-22. doi: https://doi.org/10.2174/138920008784220664

19. Tóth K, Csukly G, Sirok D, Belic A, Kiss Á, Háfra E, et al. Optimization of clonazepam therapy adjusted to patient's CYP3A Status and NAT2 genotype. Int J Neuropsychopharmacol. 2016;19(12):pyw083. doi: https://doi.org/10.1093/ijnp/pyw083

20. Klotz U. Pharmacokinetics and drug metabolism in the elderly. Drug Metab Rev. 2009;41(2):67-76. doi: https://doi.org/10.1080/03602530902722679

21. Seripa D, Pilotto A, Panza F, Matera MG, Pilotto A. Pharmacogenetics of cytochrome P450 (CYP) in the elderly. Ageing Res Rev. 2010;9(4):457-74. doi: https://doi.org/10.1016/j.arr.2010.06.001

22. Fiorelli K, Assini FL. The prescription of benzodiazepines in Brazil: a literature review. ABCS Health Sci. 2017;42(1). doi: https://doi.org/10.7322/abcshs.v42i1.948

Received: 2022, Oct 26
Accepted: 2022, Oct 27