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USE OF ANXIOLYTICS AND HYPNOTIC DRUGS DURING COVID-19 PANDEMIC - THE LITERATURE REVIEW

UPOTREBA ANKSIOLITIKA I HIPNOTIKA TOKOM COVID-19 PANDEMIJE – PREGLED LITERATURE

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Abstract

Anxiolytics and hypnotics are widely used drugs. First-line psychiatric indications for benzodiazepines (BZD) are alcohol/sedative-hypnotic withdrawal and catatonia, while panic disorder, general anxiety disorder, social anxiety disorder and insomnia are indications after failing of first/second-line treatments, and its use is recommended only for a short time. The spread of the SARS-CoV-2 virus influenced regular daily living, psychological, social, and economic stability. The COVID-19 pandemic has a multifactorial effect on people's mental health and has directly and indirectly influenced changing trends in the prescription, use and misuse of anxiolytics and hypnotics during the pandemic. This article will show use of anxiolytics and hypnotics in inpatients with SARS-CoV-2 infection with or without delirium, will present recommendation for BZD utilization in the infected individuals and will review interactions between BZD and antiviral drugs. Moreover, it will summarize available data on the frequency and reasons for use and abuse of BZD in the general population during the pandemic.

Keywords:
benzodiazepine,
anxiolytic,
hypnotic,
pandemic,
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Sažetak

Anksiolitici i hipnotici su lekovi koji se široko koriste. Glavne psihijatrijske indikacije za benzodijazepine (BZD) su odvikavanje od alkohola/sedativa-hipnotika i katatonija, dok su kod anksioznih poremećaja ili nesanice indikovani samo kratko, ukoliko je lečenje metodama prvog i drugog izbora bilo neefikasno. Širenje virusa SARS-CoV-2 uticalo je na svakodnevni život, psihološku, socijalnu i ekonomsku stabilnost. Pandemija COVID-19 je multifaktorski uticala na mentalno zdravlje ljudi, a direktno i indirektno uticala je na promene trendova u propisivanju anksiolitika i hipnotika, kao i na njihovu upotrebu i zloupotrebu. U ovom članku najpre će biti prikazana primena anksiolitika i hipnotika kod hospitalno lečenih pacijenata zaraženih SARS-CoV-2 virusom sa/bez delirijuma, preporuke za primenu BZD kod zaraženih pojedinaca, kao i prikaz interakcije između BZD i antivirusnih lekova. Pored toga, sumiraće se dostupni podaci o učestalosti korišćenja i razlozima upotrebe i zloupotrebe BZD u opštoj populaciji tokom pandemije.

Ključne reči:
benzodijazepini,
anksiolitici,
hipnotici,
pandemija,
COVID-19

Introduction

The history of contemporary anxiolytics and hypnotics begins in the mid-1950s, thanks to Dr Leo Sternbach, who discovered a new class of biologically active agents 1,4 benzodiazepines (BZD). Following the registration of the first BZD (chlordiazepoxide Librium) in 1960, many other BZDs were discovered and registered (1, 2). It became the most prescribed medication in the world in the 70's (2). In the next period, following Food and Drug Administration (FDA) and several controlled clinical trials, observed side effects of BZD influenced the utilization and it slowly declined due to rising perception of risks in their use (2, 3). In the early 90's, a group of "non–benzodiazepine" drugs (Z-drugs) was produced with the intention of treating sleep disorders. However, it later turned out that, similarly to BZDs, they have severe cognitive side effects and the potential to provoke abuse and addiction in their users (3, 4). In 2017, according to Votaw et al. (5), BZDs and other tranquilizers were the third most commonly misused illicit or prescription drugs in the US (approximately 2.2% of the population) and its misuse was associated with different negative outcomes, including mortality, low quality of life, criminality, etc. Therefore, in September 2020, the FDA updated the warnings to be implemented for BZD drug class and warned of the risk of abuse, misuse, addiction, dependence, and withdrawal (6). Also, a few years earlier, the FDA issued its highest warning that practitioners must not co-prescribe opioids and BZD since BZD were the most common drugs involved in prescription opioid overdose deaths by suppressed breathing, especially in the US (7).

They provide short-term relief from distressing feelings, yet their use should be limited to a 2 – 4 week period. First-line psychiatric indications for benzodiazepines are alcohol/sedative-hypnotic withdrawal and catatonia, while panic disorder, general anxiety disorder, social anxiety disorder and insomnia are indications after failing first/second-line treatments (2, 3). According to Guina et al. (3), several factors increase the likelihood of BZD being prescribed to an individual, such as post-traumatic stress disorder (PTSD) (8), substance use disorder, concurrent opioid prescriptions (3), the number of physical traumas (9), etc. It is important to notice that the use of BZDs after emotional trauma is controversial. If someone is using BZDs to escape reminders of a traumatic event, there is an increased risk of not learning how to manage stress. Moreover, there is also some evidence that using BZDs in patients with recent trauma can even increase the risk of developing PTSD (10).

In December 2019, the novel infectious agent SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) appeared in Wuhan (China) (11). According to the latest data by the WHO, by November 24, 2021, over 250 million people have been infected with this virus globally and 5 million people have lost their lives since the beginning of the pandemic (12). Due to the rapid transmission of this human-to-human virus, the pandemic has required many countries around the world to implement strict public-health measures to mitigate the spread of the SARS-CoV-2 virus which seriously disrupts regular daily living, psychological, social, and economic stability (13, 14). The impact of the COVID-19 (C-19) pandemic on mental health usually involves a combination of biological, psychological, and social factors (15).

COVID-19 infection, inpatients and BZD use

During the C-19 pandemic, an increased need for psychiatric consultations in general hospitals has been observed, with the highest demand for consultation in people with behavioral disorders and emotional symptoms. In addition, it was discerned that there were significant differences in psychiatric characteristics between critically ill patients and mild/moderate C-19 patients, reflecting that the more severe C-19 is, the greater the possibility of comorbid mental health problems (16).

For the first time, the frequency of BZD use in inpatients with C-19 was analyzed in Shanghai (16) at the onset of the C-19 pandemic. Out of the 329 hospitalized patients with C-19, 25.5% received psychiatric consultation suggesting a high risk of developing mental health problems. The number of psychiatric consultations was the largest in critically ill patients and the middle age group and the most common symptoms were the following: sleep disturbances (75%), anxiety symptoms (58.3%),

and depressive symptoms (11.9%); while the most common psychiatric diagnoses were: acute stress reaction (39.3%), sleep disorders (33.3%) and anxiety disorders (15.5%). More than half of the patients with C-19 infection who received psychiatric consultation were prescribed non-benzodiazepine sedative-hypnotic agents (54.8%), while BZDs were prescribed in 22.6%. The authors consider that anxiolytic-hypnotics drug treatment, which followed the principle of short-term, low-dose, and gradual titration according to the patients' condition, is a preferred choice in this unique situation which is the C-19 pandemic, even though anxiolytic-hypnotics are "back-up" drugs.

Delirium is very common in severe cases of C-19 infection and its multifactorial mechanisms are still being investigated (17-19). The use of BZD for treating delirium is controversial since there is a possibility that BZD can worsen delirium and cause paradoxical behavioural dysregulation (17). Scholars such as Baller E. et al. (17), after a synthesized narrative review of the literature and clinical experience, emphasized one particular BZD – lorazepam, for the treatment of acute agitation associated with delirium. This BZD should be combined with haloperidol in cases of C-19 which allows for greater sedation and lower risk of extrapyramidal symptoms and is also in line with the cases of non-COVID agitations. Melatonin, alpha-2 adrenergic agents and low-potency antipsychotics have been listed as first-choice therapy for C-19 delirium by these authors.

Co-prescription of BZD with antiviral drugs (ritonavir and lopinavir) for severe and critical patients with C-19 has clinical significance because of their pharmacokinetic interaction (20, 21). There is a risk of respiratory depression caused by increasing levels of BZDs such as midazolam and triazolam when they are combined with ritonavir/lopinavir due to CYP450 inhibition (22). The exceptions are lorazepam and oxazepam since the liver does not metabolize them, and they represent a safer option in combination with the aforementioned antiviral drugs (20).

An interesting finding was published by Vila-Corcoles et al. (23) who investigated C-19-related and all other causes of mortality among 79, 083 middle-aged and older adults in Southern Catalonia. The study examined a possible association between previous conditions (demographic, comorbidities, chronic medication use) and risk of death (C-19-related and/or any cause) from the electronic primary care clinical records and demonstrated that deaths from C-19 represented 21.5% of all-cause mortality occurred across the study period. According to the results, an increasing age, male sex, some pre-existing comorbidities and chronic medication use, especially BZDs (HR: 1.34; 95% CI: 1.11–1.61; p = 0.003), were associated with an increased risk of death.

The most dangerous side effect of benzodiazepines is respiratory depression, which occurs only when BZDs are co-ingested in significant quantities with alcohol or other sedative drugs (24). In addition, if there is already impaired ventilation due to comorbidity (sleep apnea or severe COPD) with a certain degree of respiratory depression, the use of BZDs can be life-threatening (2, 24). It was also experimentally proven that the use of BZDs leads to disruption of the immune system (25) that can worsen pneumonia (24–26) which should be taken into consideration during the C-19 pandemic. The mechanism by which BZDs influence to reduce bacterial phagocytosis during infection and increase susceptibility to pneumonia is through a fundamental change in macrophage physiology (increasing the number of GABA receptors and via cytoplasmic acidification). Macrophages expressed the same GABA receptors (α1β2γ 2 GABA-A) through which BZDs exert their sedative effect. Therefore, it is unclear whether the sedative actions of GABAergic drugs (such as BZDs) can be separated from their immunological effects (25).

National Health Service provided the recommendation for BZD use in C-19 (NHS, United Kingdom) emphasizing that BZDs can be used for patients with C-19 infection for acute mental health disturbance (e.g. in delirium, for rapid tranquillization) but in the lowest dose and for the shortest time possible with monitoring of respiratory function each hour until stable respiratory parameters are achieved. Patients who are exhibiting respiratory symptoms should be offered non-benzodiazepine sedating drugs first because of concern that BZDs may cause respiratory depression. Still, if this treatment is not effective, short-acting BZDs (like lorazepam) may be used as suggested above. Also, when respiratory arrest/depression is known to be caused by BZDs alone, the use of reversal agent flumazenil is necessary (24).

COVID-19 pandemic, general population and BZD use

Numerous studies worldwide have examined the impact of the C-19 pandemic on mental health and, due to the application of different methodologies (representative national samples/regional samples, structured diagnostic interview/screening instruments) and different timing of the research following the pandemic outbreak, various results are presented (15). Some of the studies record an increase in the prevalence of mental disorders in the general population (27), especially the anxiety spectrum disorders (28), and this occasion may affect the psychotropic medication utilization during the current pandemic.

Since social distancing has been mandated, Canadians have reported a worsening of their mental health (29). Amid the first wave of the pandemic, a pilot study by Yu et al. (29) was conducted in Ontario, to examine pharmaceutical trends in the prescribing and dispensing of psychotropic drugs – antidepressants (SSRI and SNRI), BZDs, and Z-drugs. Comparison of data derived from the first five months of 2020 to the same period in 2019 has shown an increase in BZDs utilization. Namely, there was a 43.7% increase in BZDs dispensing in the given period of 2020 compared to 2019. The dispensing in 2020 increased more in older than in younger population, however, no sex

differences were detected. This was different in comparison to the 2019 data when females were dispensed with more BZDs than males (p = 0.002).

A similar study was conducted in Northern California (30) but with different results. Hirschtritt and collaborators analyzed prescribing trends for commonly used psychotropic medication classes before, and following the C-19 pandemic outbreak, using electronic health records. Compared to prior-year patterns, there was a slight decrease in new and continued fills of BZDs and hypnotics medication in March – June 2020. According to this study (30), BZD fills had relatively decreased in all age groups, whereas hypnotic fills had reduced in older adults (29). Other authors found a marked increase in first BZD prescribing for older persons in April 2020, after which rates gradually returned to expected levels. The increase in BZD prescribing in patients aged 80+ could be related to increased anxiety, fear of C-19 infection, changes of care in the home environments, etc. (31). If prolonged or insufficiently controlled, BZD use in elderly increase the risk of cognitive decline (and dementia) and failures (and fractures) (2).

Studies by Yu et al. (29) and Hirschtritt et al. (30) were conducted at the beginning of the pandemic and during a lockdown period. The United States (US) cohort study (32) of approximately 15 million adults explored trends in prescribing three classes of psychotropic medications (BZD, Z-drugs, SSRI & SNRI) and how they differed by sex during the first year of the pandemic, covering its first and second wave. This study used data from one of the largest commercial health insurance databases in the US, which can indicate a population with better socioeconomic status. Throughout the first and second waves of the pandemic, the results of this study indicate an increase in Z-hypnotic prescriptions in both men and women, especially in the older population (> 65 years), which is concerning given the increased risk of adverse outcomes. It was recognized that Z-hypnotic prescriptions were more frequent in women who had a faster increase in the monthly prescription rate of Z-hypnotics and women had an increase in BZD prescriptions at the pandemic outbreak. A possible reason for woman preponderance is a higher prevalence of risk factors known to intensify during a pandemic such as pre-existing depressive and anxiety disorders (33, 34). Likewise, studies from China during the initial phase of the C-19 pandemic have found that females had higher self-reported levels of stress, anxiety, depression, and posttraumatic stress symptoms (34, 35).

The results of these studies may have been influenced by the time frame in which the studies were performed. Almost two years have passed since the start of the pandemic, so there is a possibility that individuals improved coping with the circumstances and learned how to continue their everyday life with the pandemic, in contrast to the immediate impact of the lockdown. The introduction and subsequent easing of C-19-related mitigation measures, vaccination and access to health services could had also potentially affected the rate of psychiatric medication prescriptions.

During the pandemic, the population exposed to harmful psychosocial effects was not always in a position to find mental health help due to the not available services in many regions (36). For example, the pandemic negatively influenced environment of persons with intellectual disability and/or autism spectrum disorder – closure of day centers, inability to access community for routine activities, with consequent potential impact on their mental health and behaviors. According to Rauf et al. (37) hypnotics and anxiolytics were the most commonly prescribed psychotropic medications during the lockdown period in this patient population in UK.

The misuse of BZD presents the use of medication differently than prescribed (e.g. higher doses, increased frequency, combined with alcohol, etc.), obtaining medication from several providers, or giving, selling, or trading medication to others (3). Interestingly, health-related research examining Google-search for the keywords representing BZD during the lockdown showed a significant increase in online search interest for this medication in India (38). For these reasons, BZD misuse cannot be ruled out. Before the pandemic, misuse without a prescription was the most common type of BZD misuse among younger adults; still, older adults were more likely to use their BZD more often than prescribed. In both ages, the main reasons for BZD misuse were anxiety and sleep problems. Also, BZD is typically co-abused with other substances, especially opioids (39).

The reasons for the misuse of many drugs during the C-19 pandemic, including BZDs, are provided by the national qualitative assessment by Ali et al. (40), who conducted semi-structured telephone-based interviews with adults who use drugs across Canada. Among 196 users, nearly half indicated that they had increased use of stimulants, opioids, cannabis, alcohol, hallucinogens and BZDs since the beginning of the C-19 pandemic. Some of the most common reasons for this change were related to the loss of employment or fear of catching the virus. The participants also mentioned other reasons: experience of 'boredom' due to having to self-isolate and socially distance from others; increase in use as a coping mechanism to deal with the negative physical, mental and social impacts of the pandemic; increase in use due to self-medicating, where substances are used to induce sleep or numb mental or physical pain. Also, in France, misuses of anxiolytics and hypnotics were reported particularly in the lockdown period as a consequence of social isolation (41).

A study conducted in the US by de Dios C. et al. (42) examined whether there was a change in prescription patterns of controlled medications (BZDs and opioid dispensations) at the onset of the C-19 pandemic using data from the Bamboo Health Prescription Drug Monitoring Program from 38 states (PDMP is an electronic database that tracks controlled substance prescriptions in a state). The results of this study suggest an increase in BZD dispensations in 2020 compared to 2019, and a 2% increase in the year 2020 after the onset of the actual pandemic.

Interestingly, a decrease in opioid prescriptions following the emergency declaration was detected, which may be explained by disruptions to outpatient and hospital clinical services and elective surgeries mandated during the early phase of the pandemic.

These preceding findings are consistent with the conclusions of the survey by Jones et al. (43), which used nationally representative data to assess dispensing patterns of selected substance use and mental health medication in the US from January 2019 through May 2020. The number of dispensed BZDs moved significantly above projected estimates shortly (in March), and then it was sustained within the anticipated estimates during April – May 2020.

Research done in Texas (44) presented different outcome. The restriction of elective medical procedures in March 2020 due to the C-19 pandemic, including routine office visits, was associated with a significant decline in prescribers writing and patients filling opioid and BZD prescriptions compared to the period before the pandemic. This decline indicated a care gap for these patients during the first wave of the pandemic.

According to the recent review by Sarangi et al. (36), five out of eight larger studies conducted worldwide showed an increase in BZD use, whereas two have reported a decrease, which indicates that pandemic has been associated with changing trends in BZD prescription, use and misuse during the pandemic. One of the factors for differences in BZD utilization is the existing differences in BZD prescription regulation around the world (45). For instance, many countries in the US have implemented PDMPs that represent state-level interventions to help changes in prescribing behaviors, prevent adverse drug-related events through opioid overdoses, drug diversion, and substance abuse (46).

Due to the risk of abuse, 35 registered BZDs have been placed under control by the Convention on Psychotropic Substances since 1971, insisting on dispensing exclusively by prescription (45). At that time, consequences of such immediate strict regulations induced increased use of uncontrolled substances such as alcohol, however, shortly afterward the control yielded positive results and was followed by many well-organized health systems worldwide. However, official regulation of BZD prescription in Serbia is still allowing long-term prescription of BZD (up to 3 months) by a general practitioner and its unlimited continuation upon specialist approval (47), which could be regarded as a risk factor for non-rational (although prescribed) BZD use. In addition, the non-prescribed use of BZD in the country is another important issue (48). Due to severe risks associated with irrational and unresponsive use of BZD, it is important to conduct studies based on the representative population of Serbia, to elucidate BZD use during the pandemic, and to plan public health interventions where needed.

Conclusion

The sudden onset of the current C-19 pandemic has led to the overcoming of emerging socio-economic, political and public health difficulties and the health care system particularly has been intensively adapting to the course of the pandemic.

The guidelines for the use of BZD in inpatients treated due to C-19 infection do not differ from those regularly used in the intensive care unit. The use of BZD in the general population during the current pandemic has not been studied sufficiently, and the existing results are contradictory. They indicate both an increase and a decrease in use, which may be influenced by various factors – from sociodemographic factors, public health care regulations, to the phase of the pandemic when the results have been collected.

Subsequent research should focus on the utilization as well as misuse of anxiolytic-hypnotic drugs in order to improve their rational use and to prevent the epidemic of BZD use during and after the C-19 pandemic.

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