European Monitoring Centre
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PERSPECTIVES ON DRUGS

The misuse of benzodiazepines among high-risk opioid users in Europe

Benzodiazepines are a widely prescribed group of medicines with a range of clinical uses, including the treatment of anxiety and insomnia and the management of alcohol withdrawal. For a number of reasons this group of medicines are often misused by high-risk opioid users and are associated with morbidity and mortality among this group. This analysis considers the significance of this problem and its impact for the health and drug treatment of opioid users.

Full edition of this article with interactive features available online at

emcdda.europa.eu/topics/pods/benzodiazepines

Introduction

Benzodiazepines have a range of clinical uses and are one of the most commonly prescribed medicines globally. They have proven useful in treating a range of health problems including anxiety, insomnia and alcohol withdrawal (Medicines and Healthcare Products Regulatory Agency, 2014). However, like all medicines, there can be side effects associated with benzodiazepine use, in particular with the misuse of these medicines, which for the purposes of this analysis we define as use without a prescription from a medical practitioner or with a prescription but outside of accepted medical practice or guidelines.

While the misuse of benzodiazepines has been identified as a concern for a number of groups in the general population, e.g. among the elderly and women, this analysis focuses specifically on the misuse of benzodiazepines among high-risk opioid users ([1]), a group where these medicines have been linked with severe treatment challenges and implicated in high levels of drug-related deaths.

It is important to stress that much benzodiazepine prescribing to high-risk drug users is for legitimate therapeutic purposes. Nevertheless, there are concerns relating to unintended health consequences associated with the use of benzodiazepine for longer periods (e.g. more than two to three weeks), polydrug use, and use that is not in accordance with prescribing guidelines.

([1]) A definition of high-risk opioid users is available on the EMCDDA website (www.emcdda.europa.eu/attachements.cfm/att_218205_EN_PDU%20revision.pdf).

As we describe below, available evidence shows that the misuse of benzodiazepines contributes to morbidity and mortality among high-risk opioid users. This includes a greater risk of heroin overdose, as well as being associated with a higher risk of human immunodeficiency virus (HIV) infections, psychopathology (anxiety and depression), poorer treatment outcomes and poorer social functioning (Darke et al., 1995; Lader, 2012; Ford and Law, 2014).

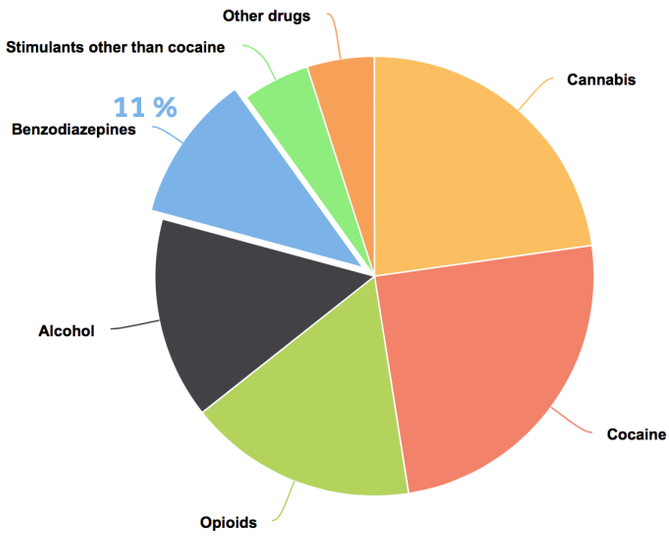
Benzodiazepine misuse among high-risk opioid users

High-risk opioid users typically misuse benzodiazepines to self-medicate or to increase the effects of opioids (Vogel et al., 2013). Users self-medicate to treat psychiatric disorders and negative emotional states (anxiety, insomnia) and to alleviate opiate withdrawal symptoms or the adverse effects of drugs like alcohol or cocaine. Benzodiazepines can also prolong the intensity and duration of the effect of opioids, especially when injected. Patients in opioid substitution treatment (OST) with methadone, for example, may misuse benzodiazepines to increase the effects of their opioid medication (Jones et al., 2012). Reports suggest this practice may be correlated with an under-dosing of the substitution treatment, which results in the re-emergence of withdrawal symptoms (Chen et al., 2011).

Benzodiazepines are generally taken orally, snorted, and by intravenous injection among high-risk opioid users. While a wide variety of types of benzodiazepines are available and misused in Europe by high-risk opioid users, those most commonly reported in studies or identified in statistics of drug-related deaths are diazepam, clonazepam, alprazolam, oxazepam and flunitrazepam. Benzodiazepines with a more rapid onset of action (e.g. diazepam, alprazolam or lorazepam) appear to be more frequently used by opioid users than those with a slower onset (e.g. oxazolam or prazepam).

Users obtain benzodiazepines from different sources, including diversion of prescriptions (such as 'doctor shopping' ([2])), the illicit market and the Internet. A growing number of benzodiazepines that are not approved medicines within the European Union (EU), such as flubromazolam or flubromazepam, have been identified for sale at street level and online.

Figure 1. Substances reported as their secondary drug by clients entering drug treatment for primary opioid problems



While treatment demand data ([3]) do not allow us to gauge the full scale of benzodiazepine misuse, it does give an important insight into the scope of the problem. Data show that the combined use of opioids and benzodiazepines is a significant issue among those receiving treatment. Available data for 2014 from 18 countries ([4]) where opioids were reported as the primary problem drug ([5]) by those entering treatment (102 000, or 19 % of all clients) show benzodiazepines were reported as a secondary problem drug ([6]) by 11 %, or 10 000 of those entering treatment. Higher levels were reported in some countries, ranging from 30–50 % of those entering treatment. However, it should be noted that secondary drugs, including benzodiazepines, are often under-reported.

The prevalence of benzodiazepine misuse among clients in OST ranges from 45 % in France (Brisacier and Collin, 2014) to 70 % in Germany (Specka et al., 2011; Laqueille et al., 2009). The frequency of benzodiazepine misuse among those undergoing OST is reported to increase with the length of treatment (Fernández Sobrino et al., 2009). This factor has also been identified in other treatment outcome studies (Comiskey, 2013; Stewart et al., 2002). High rates of benzodiazepine misuse have also been found among high-

([2]) 'Doctor shopping' refers to the practice of a patient requesting care from multiple physicians, often simultaneously, without making efforts to coordinate care or informing the physicians of the multiple caregivers. This usually stems from a patient's addiction to, or reliance on, certain prescription drugs or other medical treatment.
([3]) European countries provide data according to the same protocol (treatment demand indicator standard protocol 3.0) on the characteristics and patterns of drug use of people entering drug treatment for problems related to their drug use (www.emcdda.europa.eu/publications/manuals/tdi-protocol-3.0).
([4]) Data from 18 of 30 countries: Belgium, Bulgaria, the Czech Republic, Ireland, Greece, Croatia, Italy, Cyprus, Malta, Netherlands, Austria, Portugal, Romania, Slovenia, Slovakia, Finland, the United Kingdom and Turkey.
([5]) The primary drug is defined as the drug that causes the client the most problems at the start of treatment. This is usually based on the request made by the clients and/or on the diagnosis made by a therapist, commonly using international standard instruments (e.g. ICD-10; DSM-IV; ASI) or clinical assessment. This item is of central importance and it should be collected for every client. Secondary drugs are those drugs used in addition to the primary drug, and are substances that cause problems for the client and/or change the nature of the problem as assessed by the client and the therapist (www.emcdda.europa.eu/publications/manuals/tdi-protocol-3.0).
([6]) A secondary drug should be recorded 'only if it causes problems to the client according to the client's request and to the professional's assessment' (TDI version 3.0).

Facts and figures

Benzodiazepines were introduced into clinical medicine in the early 1960s. They rapidly replaced barbiturates as sedative-hypnotics because they were safer, particularly because they were less likely to cause fatal central nervous system depression (Longo and Johnson, 2000; EMCDDA drug profile).

Benzodiazepines act as central nervous system depressants by enhancing the actions of the neurotransmitter GABA (gamma-aminobutyric acid). This has a calming effect on many functions of the brain, including inducing sedation and sleep (Lalive et al., 2011).

They are used for treating psychiatric and neurological conditions, including insomnia, anxiety disorders, alcohol dependence and epilepsy. Some are also used as a pre-anaesthetic and intraoperative medication (Medicines and Healthcare Products Regulatory Agency, 2014).

Benzodiazepines can be divided into different groups based on their chemical structure and pharmacokinetic properties, although they share a common mechanism of action and produce similar pharmacological effects (Baldwin et al., 2013).

Based on their pharmacokinetics, benzodiazepines can be placed into one of three groups. These are: short-acting agents, with half-lives of under six hours (e.g. oxazepam), intermediate-acting agents with half-lives of 6–24 hours (alprazolam), and long-acting agents with half-lives of over 24 hours (diazepam) (Medicines and Healthcare Products Regulatory Agency, 2014).

risk opioid users in prisons, with one study involving 38 Italian prisons finding that 85 % of opioid users were misusing benzodiazepines (Nava, 2014). Current data on trends in benzodiazepine misuse among high-risk opioid users in treatment indicate a relatively stable trend between 2006 and 2013, with a decrease in the last year.

The majority of reported benzodiazepine misuse occurs among those reporting opioid use as the primary drug for which they are entering treatment. However, around 7 000, or 2 % (range: 0–20 %), of all clients entering treatment reported benzodiazepines as the primary drug of misuse; and 20 % of these clients also reported the use of opioids as a secondary drug. Ireland, Finland and Romania are the countries with the highest rates, where more than 5 % of treatment clients reported benzodiazepine use as their primary drug problem.

Health harms

There is evidence of various harms associated with benzodiazepine misuse among both the general population and in particular vulnerable groups including high-risk opioid users. This can include problems associated with rapid tolerance, dependence and withdrawal. In the latter case this can include increased anxiety, agitation, confusion and panic attacks, and can lead, in vulnerable people, to acute psychosis. Abrupt withdrawal can cause uncontrollable and potentially fatal convulsions (Jones et al., 2012; Ashton, 1986). The cessation of benzodiazepine use is complex and requires medical support, which can include the use of other medications to manage withdrawal or provide substitution. Sometimes this process might need to take place in an inpatient setting.

The use of benzodiazepines has been linked with long-term effects including over-sedation, depression and immune system problems. As side effects can be more pronounced in the elderly, Europe's ageing population of chronic opioid users are at extra risk. Polydrug use involving opioids and benzodiazepines can also expose users to other risk behaviours and drug-related harms. These include needle-sharing, using higher doses of drugs, intoxication-related accidents, and poor physical and psychological health (Vogel et al., 2013; Lavie et al., 2009; Rooney et al., 1999).

Studies suggest that opioid users who use/misuse benzodiazepines experience a high level of health problems and use health services frequently. For example, the Australian Treatment Outcome Study (ATOS) (Darke et al., 2003) looked at the relationship between use of healthcare services and benzodiazepine misuse among heroin users. It found that heroin users who also used benzodiazepines had frequent general practitioner (GP) and psychiatrist visits, were more likely to have had an ambulance attendance and had significantly more dispensed prescriptions than other heroin users. A recent study in France among patients on buprenorphine explored the co-prescription of benzodiazepines on opioid treatment outcomes; although no impact on outcome was identified, benzodiazepine prescription was associated with more frequent emergency department visits and accidental injuries (Schuman-Olivier et al., 2013).

Interactive element: video

Video on misuse of benzodiazepines among high-risk opioid users, available on the EMCDDA website: www.emcdda.europa.eu/topics/pods/benzodiazepines

Overdose

Simultaneous use of opioids with benzodiazepines and other central nervous system depressants, such as alcohol, increases the risk of non-fatal and fatal overdose through respiratory depression (White and Irvine, 1999).

The increased risk of overdose among opioid users is reflected in the high frequency of benzodiazepines identified in post-mortem examinations of drug-related death cases. For example, benzodiazepines were identified in 40–80 % of methadone-related deaths (France, United States, Australia) and in 50–80 % of heroin-related deaths (Germany, Ireland, United Kingdom) (Lintzeris et al., 2007). Current European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) drug-induced deaths data show that benzodiazepines were implicated (i.e. they were thought to have played a role in the death) in 28 % of deaths in Scotland ([7]), 48 % in France, 30–32.5 % in Portugal ([8]) and 35 % in Ireland ([9]). In addition, when the presence of benzodiazepines is considered in drug-induced deaths, percentages have been reported for Scotland (72 %) ([10]) and Finland (88 %) ([11]). It is, however, important to note that that even when benzodiazepines were not implicated in deaths, they may have played a role in risk behaviours that led to death.

Insights from hospital emergency departments

Data from hospital emergency departments provide valuable insights into drug user and related health problems. This information can be used as a leading edge or real time indicator of drug problems. The European Drug Emergencies Network (Euro-DEN) project is a European Commission Drug Prevention and Information Programme funded project that involves longitudinal collection of data from 16 sentinel centres in 10 European countries on emergency department presentations with acute drug and NPS toxicity (Wood et al., 2014).

The Euro-DEN database was searched to identify cases from 1 October 2013 to 30 June 2014 where heroin had been used prior to presentation. Of the 3 573 Euro-DEN cases over this nine-month period, 872 (23.2 %) involved self-reported use of heroin. Of these, 221 (25.3 %) had also used one or more benzodiazepines (of which 196 (88.7 %) involved one benzodiazepine, 21 (9.5 %) involved two benzodiazepines and 3 (1.8 %) involved three benzodiazepines) (Dargan et al., 2015).

There was significant variation across the Euro-DEN centres, ranging from no heroin presentations in Barcelona, Copenhagen and Paris involving a benzodiazepine to 35.6 % of heroin presentations in Oslo involving a benzodiazepine. There was no significant difference in the age or gender of the heroin–benzodiazepine cases and the heroin cases not involving a benzodiazepine, and there was no difference in the proportion with coma. However, those in the heroin–benzodiazepine group had a longer stay in hospital (5 hours 46 minutes versus 4 hours 45 minutes, p=0.03) and were more likely to be admitted to critical care.

There have been case reports of fatal poisonings involving mixing benzodiazepines with buprenorphine in France, where buprenorphine is more commonly used than methadone for substitution treatment, with benzodiazepines identified in 70 % of buprenorphine-related deaths (France, special mortality register data, DRAMES 2012; Reynaud et al., 1998). While buprenorphine causes less respiratory depression than methadone, non-clinical studies have found that its ceiling effect on respiratory depression is removed when combined with benzodiazepines (Nielsen and Taylor, 2005). For all opioids, establishing the role of benzodiazepines in drug-related deaths is complicated by several factors. For instance, the combinations of drugs identified are often complex, individuals have different levels of tolerance and metabolisms, and a level of subjectivity exists in toxicological assessments.

([7]) 'Drug-related deaths in Scotland 2013', published by National Records Scotland (www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/deaths/drug-related-deaths-in-scotland/2013).
([8]) Two data sources have been used to illustrate the situation in Portugal, the Special Mortality Register and the General Mortality Register.
([9]) As was illustrated by recent data from a number of countries during the latest annual drug-related deaths experts' meeting (www.emcdda.europa.eu/expert-meetings/2014/drd-drid).
([10]) 'Drug-related deaths in Scotland 2013', published by National Records Scotland (www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/deaths/drug-related-deaths-in-scotland/2013).
([11]) See note 10.

Challenges for the future

Benzodiazepines have a range of well-established clinical uses and side effects. This makes their widespread availability and the potential for misuse a serious problem, particularly where they are taken by opioid users as part of polydrug use repertoires. The picture that emerges from research studies and the available epidemiological data presents a challenging situation. Benzodiazepines have a role in the management of the mental health issues opioid users experience from their drug consumption. However, the misuse of benzodiazepines with other drugs can expose users to a spectrum of problems ranging from mental health issues, compromised treatment outcomes and risky drug consumption practices, to more severe consequences such as non-fatal and fatal overdoses. To date, however, benzodiazepine misuse alongside other drugs among high-risk opioid users has often been viewed by users and service providers as a secondary issue, neglecting its polydrug use dimension and consequences. The situation is further complicated by the emergence of new benzodiazepines on the illicit market in some countries, for example, phenazepam and etizolam, which have been implicated in several deaths among opioid users in Scotland ([12]). With a continuing need to use benzodiazepines for various medical purposes and in order tomitigate the risks opioid users taking them face, prescribing and clinical practice guidelines have a critical role to play in the management of this issue as part of a comprehensive response to polydrug users among high-risk opioid drug users. Giving the ageing nature of this population within Europe and the increased potential for health complications from ongoing drug use, this issue is an existing challenge that treatment systems must address.

Guidelines for prescribing benzodiazepines to opioid users

There are only a few evidence-based clinical guidelines available to support practitioners on the use and management of benzodiazepines among high-risk opioid users. The EMCDDA's Best Practice Inventory (www.emcdda.europa.eu/best-practice) currently contains six sets of guidelines that address these issues, as part of general or specific guidelines for managing opioid use.

The Substance Misuse Management in General Practice guidance in the United Kingdom, which specifically addresses the use and reduction of misuse of benzodiazepines and other hypnotics and anxiolytics, proposes a strategic course of action:


photo: iStock

Strategy for prescribing benzodiazepines to opioid-dependent patients:

1. Treat the opioid dependence first; this has a good evidence base.

2. Discuss with patients how they will control and reduce their benzodiazepine use themselves (without the need for a benzodiazepine prescription). Many patients are able to reduce their illicit supply themselves.

3. Re-assess patients' benzodiazepine use once they are stable on their opioid prescription and it has been optimised. Clinical experience shows that benzodiazepine use (even what clinically appears to be dependence) often ceases once on a stable opioid substitution.

4. If use of benzodiazepines is continuing, reassess the reasons. Is it for sedation, the 'buzz', anxiety or the comedown from crack or other drugs? Does it enhance the opioid 'buzz'? Do not prescribe benzodiazepines if use is for pleasure or in binges.

5. If dependence on benzodiazepines is present, consider a short term (six weeks to six months) reducing prescription of benzodiazepines on daily pickup (a minimum of six days a week).

6. Stop the benzodiazepine prescription if persistent illegal benzodiazepine use or alcohol dependence are present.

7. Consider similar staged detoxification as with other patients dependent on benzodiazepines.

([12]) Most drug-induced deaths in Scotland involving benzodiazepines were linked to diazepam, but phenazepam, which was placed under control in the United Kingdom in 2012, and etizolam, which is not controlled, were also implicated in several deaths.

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