European Monitoring Centre
for Drugs and Drug Addiction

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 that include treating anxiety, insomnia and managing alcohol withdrawal. This group of medicines is often misused by high-risk opioid users, and this is associated with considerable morbidity and mortality. This paper describes the impact of benzodiazepines misuse on the health and treatment of high-risk opioid users.

Introduction

Benzodiazepines have a range of clinical uses and are among the most commonly prescribed medicines globally. They are useful in the short-term treatment of anxiety and insomnia, and in managing alcohol withdrawal (Medicines and Healthcare Products Regulatory Agency, 2015). Like all medicines, benzodiazepines can produce side effects. They may also be misused, which we define as use without a prescription from a medical practitioner or, if prescribed, when they are used outside accepted medical practice or guidelines.

While the misuse of benzodiazepines has been identified as a concern for large groups in the general population, for example, among elderly people and women, this analysis focuses specifically on misuse among high-risk opioid users [1], a group of people among whom these medicines have been linked with severe treatment challenges and implicated in considerable numbers of drug-related deaths.

It is important to stress that much benzodiazepine prescribing to high-risk drug users is done with legitimate therapeutic aims in mind. Nevertheless, these medicines may be used in ways that produce unintended negative health consequences, especially when they are used for longer than two to three weeks, form part of polydrug use patterns — typically in combination with illicit drugs or alcohol — and are used in ways that do not accord with prescribing guidelines.
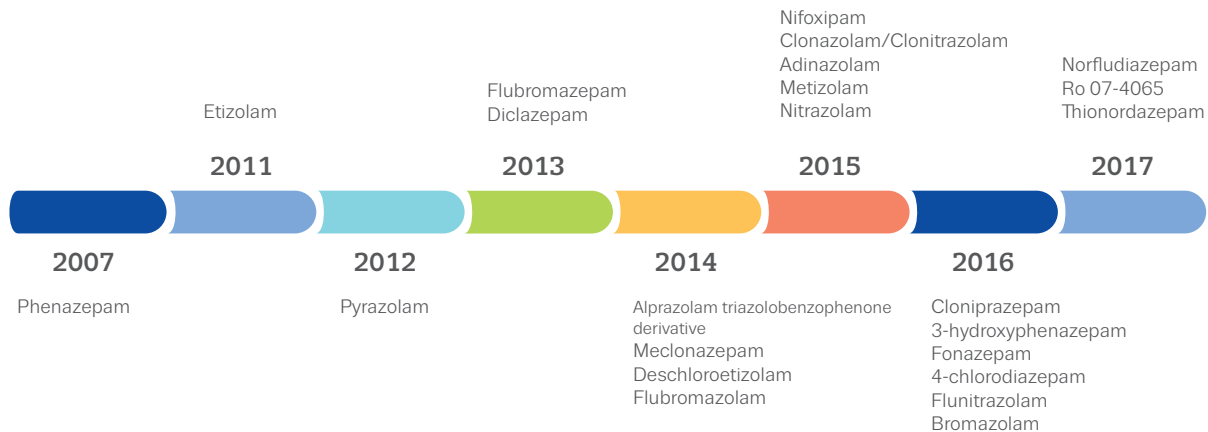
Full edition of this article with interactive features available online at

emcdda.europa.eu/topics/
pods/benzodiazepines

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[1] A definition of high-risk opioid use is available on the EMCDDA website

Figure 1. Timeline of the reporting of new benzodiazepines to the EMCDDA

As is described below, the misuse of benzodiazepines contributes to increased morbidity and mortality among high-risk opioid users. It increases the risk of opioid overdose and is associated with a higher risk of acquiring HIV infection, experiencing anxiety and depression, and having poorer treatment outcomes and poorer social functioning (Darke et al., 1995; Ford and Law, 2014; Lader, 2012).

Benzodiazepine misuse among high-risk opioid users

High-risk opioid users typically misuse benzodiazepines to self-medicate or increase the effects of opioids (Vogel et al., 2013); reasons that may overlap. They self-medicate to treat symptoms of psychiatric disorders, negative emotional states, opioid withdrawal symptoms, and the side effects of alcohol and cocaine use. Benzodiazepines, especially when injected, can prolong the intensity and duration of opioid effects. For this reason, patients in opioid substitution treatment (OST) may misuse benzodiazepines in order to increase the effects of their opioid medication (Jones et al., 2012). Such misuse may be prompted by withdrawal symptoms caused by under-dosing of the substitution treatment (Chen et al., 2011).

High-risk opioid users generally take benzodiazepines orally, by snorting or by intravenous injection. While a range of different benzodiazepines are misused in Europe, those most commonly detected in drug-related deaths are diazepam, clonazepam, alprazolam, oxazepam and flunitrazepam. This suggests that this group may prefer to use benzodiazepines with a more rapid onset of action (e.g. diazepam, alprazolam) than those with a slower onset (e.g. oxazolam, prazepam).

The type of benzodiazepines used may be influenced by a range of factors, such as personal preferences, availability and price. Shifts from one type of benzodiazepine to another have been observed after changes in legal status or other regulatory measures. In France, for example, after restrictions were imposed on flunitrazepam prescriptions, misuse of

the drug decreased while misuse of clonazepam increased (OFDT, 2005). In the United Kingdom, the withdrawal of temazepam capsules and stricter prescribing practices appears to have increased the use of diazepam (as well as 'Z-drugs') ([2]) and prompted the use of 'new' benzodiazepines, such as phenazepam and etizolam, which were not originally controlled under drug legislation (Johnson et al., 2016).

Benzodiazepines are obtained from different sources, including diversion of prescriptions (through practices such as 'doctor shopping') ([3]), the illicit market and the internet. A growing number of new benzodiazepines have been identified for sale at street level and online. In many cases, these have not been authorised as medicines within the European Union (EU), for example, flubromazolam and flubromazepam.

The increasing number of new benzodiazepines

Over the last decade, the EU Early Warning System on new psychoactive substances ([4]) has detected an increasing number of new benzodiazepines that have appeared on Europe's drug market ([5]) (Figure 1), with more than half having been detected since 2015. The first of these were phenazepam in 2007 and etizolam in 2011. Four of these drugs — etizolam, diclazepam, flubromazolam and phenazepam — account for over 80 % of all tablets containing new benzodiazepines that have been seized in Europe since 2005 ([6]). Phenazepam, which is now a controlled drug, has

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([2]) Zaleplon, zolpidem and zopiclone and related medicines (sometimes referred to as 'Z-drugs') are a group of non-benzodiazepine hypnotic drugs with pharmacology similar to benzodiazepines.
([3]) 'Doctor shopping' refers to the practice of patients requesting care from multiple physicians, often simultaneously, without making efforts to coordinate care or informing the physicians of the other caregivers. This usually stems from a patient's addiction to, or reliance on, certain prescription drugs or other medical treatment.
([4]) http://www.emcdda.europa.eu/activities/action-on-new-drugs
([5]) New psychoactive substances, including new benzodiazepines, are psychoactive substances that are not under international control. However, over time, some of these substances may be assessed as being particularly harmful and brought under control.
([6]) Based on seizure data reported to the EU Early Warning System.

been linked to hospitalisations and deaths. It can cause psychomotor impairment, respiratory arrest, psychosis and delirium. It is sold on the internet and the illicit market as a powder, tablets and blotters.
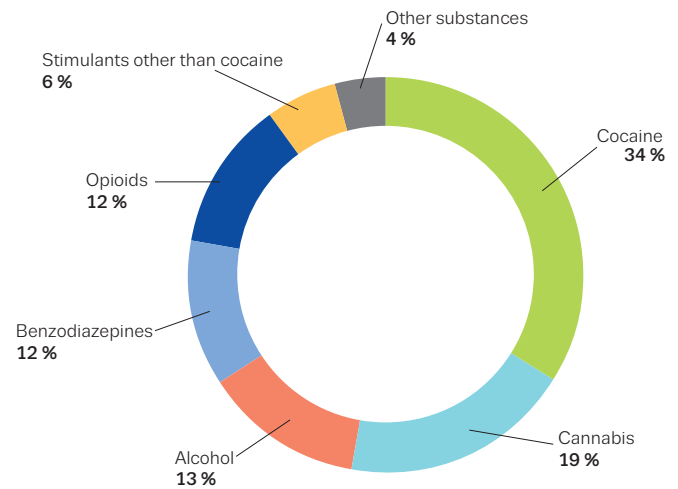
Some of the new benzodiazepines, such as phenazepam, have been approved and marketed for use in a few countries in the past, others may be found in the patent literature but have never been brought to market, and some are novel compounds. The majority have never undergone clinical trials or tests (Manchester et al., 2017). New benzodiazepines may provide an attractive alternative to prescribed benzodiazepines for misuse because they are readily available via the internet or are sold on the illicit market. Their pharmacology and toxicology is largely unknown and they may pose higher risks to users.

Another issue that has emerged is that new benzodiazepines have been found mixed with other new psychoactive substances, including synthetic cannabinoids (Couch and Madhavaram, 2012). Furthermore, counterfeit diazepam tablets have been seized in in Europe that contained a new potent synthetic opioid. These tablets pose a serious risk to users, who will not be aware that they are using a potent opioid.

Extent of benzodiazepine misuse among high-risk opioid users

Benzodiazepine misuse among high-risk drug users, like other forms of high-risk drug use, cannot be measured by direct methods, such as surveys of the general population. Insights into the scale of the problem can, however, be gained from data collected from those entering specialised drug treatment in Europe. Treatment demand data ([7]) do not allow us to gauge the full scale of benzodiazepine misuse, but they give some important insights into the scope of the problem. These data show that the combined use of opioids and benzodiazepines is reported by a considerable number of those receiving treatment. Data from 23 countries ([8]) show that, among the 42 700 treatment entrants in 2015 who reported opioids as their primary problem drug ([9]) (40 % of all clients entering treatment), benzodiazepines were reported as a secondary

Figure 2. Frequency of reporting different substances as a secondary drug by clients entering drug treatment for primary opioid problems

problem drug ([10]) by 12 000 or 12 % of the opioid clients who reported a secondary problem drug (Figure 2). Higher levels, ranging from 30 % to 50 % of those entering treatment with opioids as their primary problem drug, were reported in some countries. However, these figures are probably under-estimates because problems with secondary drugs, including benzodiazepines, are often under-reported. Data on benzodiazepine misuse among high-risk opioid users in treatment indicate a relatively stable trend between 2006 and 2013.

Other studies have found prevalence rates of benzodiazepine misuse among clients in OST ranging from 45 % in France (Brisacier and Collin, 2014) to 70 % in Germany (Laqueille et al., 2009; Specka et al., 2011). The frequency of benzodiazepine misuse is reported to increase with the length of OST treatment (Fernández Sobrino et al., 2009). This factor has also been identified in treatment outcome studies (Comiskey, 2013; Stewart et al., 2002). High rates of benzodiazepine misuse have also been found among high-risk opioid users in prisons. One study in 38 Italian prisons found that 85 % of opioid users misused benzodiazepines (Nava, 2014). A study of French male prisoners found that 37 % were chronic benzodiazepine misusers and that many high-risk opioid users switched from illicit opioids to benzodiazepines when incarcerated, either to make their incarceration bearable or to cope with withdrawal symptoms (Expertise Collective, 2012).

In addition to the 12 000 people entering treatment primarily for opioid-related problems, who also report benzodiazepines as a problem drug, benzodiazepines are reported as the primary problem drug by around 8 150, or 2 % (range: 0 to 9 %), of all treatment entrants. Of the primary benzodiazepine clients who reported a secondary drug, 36 % cited opioids as a

([7]) 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).

([8]) Data from 23 of 30 countries: Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Greece, Ireland, Italy, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Turkey, United Kingdom.

([9]) 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)

([10]) 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).

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secondary problem drug. Benzodiazepines were reported as the primary problem drug by more than 5 % of treatment entrants in three countries: Belgium, Ireland and Finland.

Health harms associated with benzodiazepine misuse

Among both the general population and vulnerable groups, such as high-risk opioid users, the prolonged use and misuse of benzodiazepines can cause a range of harms to health. These include problems associated with rapid development of tolerance, dependence and withdrawal symptoms, which can, in people who have particular vulnerability, include increased anxiety, agitation, confusion, panic attacks and acute psychosis. Abrupt benzodiazepine withdrawal can cause uncontrollable and potentially fatal convulsions (Ashton, 1986; Jones et al., 2012). The cessation of regular benzodiazepine use requires medical support and this may include the use of other medications to manage withdrawal symptoms or provide substitution. The withdrawal process may need to occur in an inpatient setting. The prolonged use of benzodiazepines has been linked with long-term adverse effects such as over-sedation, depression and immune system problems. Europe's ageing high-risk opioid users are at increased risk of side effects, which can be more pronounced in the elderly. In addition, polydrug use involving opioids and benzodiazepines can also expose users to other risk behaviours and drug-related harms, such as needle-sharing, using high doses of drugs, intoxication-related accidents, and poor physical and psychological health (Lavie et al., 2009; Rooney et al., 1999; Vogel et al., 2013).

Opioid users who misuse benzodiazepines experience a high level of health problems and frequently use health services. For example, the Australian Treatment Outcome Study (ATOS) (Darke et al., 2003) found that heroin users who also misused benzodiazepines had more general practitioner (GP) and psychiatrist visits, were more likely to have required an ambulance, and had more dispensed prescriptions than heroin users who did not. A study in France of patients prescribed buprenorphine for opioid dependence found that the co-prescription of benzodiazepines had no impact on opioid treatment outcome but was associated with more emergency department visits and accidental injuries (Schuman-Olivier et al., 2013).

Overdose

The 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 with which benzodiazepines are identified post-mortem in drug-related deaths. For example, benzodiazepines were identified in 40 to 80 % of methadone-related deaths (France, United States, Australia) and in 50 to 80 % of heroin-related deaths (Germany, Ireland, United Kingdom) (Lintzeris et al., 2007). Data reported to the EMCDDA show further evidence of the presence of benzodiazepines in a large proportion of drug-related deaths, many of which are opioid-related, for example benzodiazepines were found in 88 % of cases in Finland (Ojanperä and Kriikku, 2014), 73 % in Scotland (National Records of Scotland, 2017) and 41 % in Portugal ([11]). In addition, benzodiazepines were thought to have played a role (were implicated) in 49 % of drug-related deaths in Scotland (National Records of Scotland, 2017), 48 % in France (Mallaret, 2014) and 35 % in Ireland (Lynn, 2014). It is important to note that in some deaths, benzodiazepines may have played a role in risk behaviours that led to the death, although they were not reported to be the cause of death or as a contributing factor.

In France, where buprenorphine is more often used than methadone for opioid substitution treatment, fatal poisonings involving combinations of benzodiazepines and buprenorphine have been reported (Reynaud et al., 1998); benzodiazepines were identified in 70 % of buprenorphine-related deaths (Mallaret, 2014). While buprenorphine causes less respiratory depression than methadone, its ceiling effect on respiratory depression is removed when it is 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

([11]) Data reported by the Portuguese national focal point to the EMCDDA in 2017 (data for 2016: 11 out of 27 drug-related deaths).

Insights from hospital emergency departments

The European Drug Emergencies Network Plus (Euro-DEN Plus) project has been collecting data on presentations to sentinel emergency departments across Europe with acute recreational drug toxicity since October 2013.

The Euro-DEN Plus project analysed 16 033 presentations (involving 24 538 drugs) with acute drug toxicity over the 3-year period from January 2014 to December 2016, from 21 sentinel centres in 14 European countries. There was a total of 3 742 presentations involving acute toxicity related to the self-reported use of heroin, of these 1 851 had used only heroin while 922 had used heroin together with at least one benzodiazepine. The most frequently reported benzodiazepines associated with heroin were clonazepam, 'unknown benzodiazepine', diazepam and alprazolam.

Over the same period, the Euro-DEN Plus project recorded 2 767 benzodiazepine-related emergency department presentations (17.3 % of all Euro-DEN Plus presentations). The most commonly recorded benzodiazepine was clonazepam, followed by 'unknown benzodiazepine', diazepam and alprazolam. There were geographical differences, both in terms of the proportion of presentations involving benzodiazepines (more common in Estonia, Germany, France, Ireland and Norway; less common in Malta, Poland and the United Kingdom) and in the benzodiazepines involved (clonazepam most common in Norway, and bromazepam in France).

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

thereby neglecting the effects of polydrug use and its serious consequences.

With continuing use of benzodiazepines for various medical purposes, prescribing and clinical practice guidelines have a critical role to play in mitigating the risks opioid users taking them face. However, few evidence-based guidelines addressing the management of benzodiazepine use among high-risk opioid users are currently available. Such guidelines need to be part of a comprehensive response to polydrug use among high-risk opioid drug users. This is a challenge that treatment systems must address given that this population is ageing in Europe and have an increased risk of serious health complications from their ongoing drug use.

The situation is complicated by the emergence on the illicit market in some countries of new benzodiazepines, such as phenazepam and etizolam, which may increasingly contribute to deaths among opioid users. For example, in Scotland in 2016, such new benzodiazepines were responsible for most of the rise in drug-related deaths in which benzodiazepines were implicated or potentially contributed, and etizolam overtook diazepam as the benzodiazepine most frequently reported in drug-related deaths (National Records of Scotland, 2017). In illicit markets these substances are not only sold as benzodiazepines but may also appear as contaminants or be marketed in place of other new psychoactive substances or illicit drugs, potentially increasing the risks associated with them. In addition, in some EU countries, such as Ireland and the United Kingdom, concerns have recently been raised that the availability of extremely cheap illicit benzodiazepines, including new benzodiazepines, on the internet may be leading to increased use of these drugs by vulnerable teenagers, often in combination with alcohol. This pattern of use is reported to be linked to behavioural problems, as well as posing a risk of overdose. This highlights the need for monitoring systems and services to be alert to the potential risks associated with benzodiazepine use and how these may be changing.

instance, a complex combination of drugs may be involved, individuals have different metabolisms and levels of tolerance to different drugs, and there is some subjectivity in toxicological assessments of their role in cause of death.

Challenges for the future

Benzodiazepines are well-established medicines for a range of short-term clinical uses but they also have adverse side effects. Their widespread availability increases the potential for the misuse of these drugs to pose a serious public health problem, particularly where they are taken by opioid users as part of polydrug use repertoires. The picture that emerges from research and epidemiological data presents a challenging situation. Benzodiazepines may have a role in managing mental health issues that opioid users often experience, but their misuse alongside other drugs can increase mental health problems, compromise treatment outcomes, and increase risky drug consumption practices, leading in some cases to more severe consequences, such as non-fatal and fatal overdoses. Benzodiazepine misuse among high-risk opioid users has often been viewed by both users and service providers as an issue of secondary importance,

Facts and figures

Benzodiazepines were introduced into clinical medicine in the early 1960s. They rapidly replaced barbiturates as sedative-hypnotics because they were safer and 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). They have a calming effect on many functions of the brain and induce 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 used as pre-anaesthetic and intraoperative medications (Medicines and Healthcare Products Regulatory Agency, 2015).

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

Benzodiazepines can be placed into one of three groups based on their pharmacokinetics. These are short-acting agents, with half-lives of less than 6 hours (e.g. oxazepam); intermediate-acting agents, with half-lives of 6 to 24 hours (e.g. alprazolam); and long-acting agents, with half-lives of over 24 hours (e.g. diazepam) (Medicines and Healthcare Products Regulatory Agency, 2015).

The benzodiazepines that are under international control at the time of writing and the schedule under which they are classified are shown in the table below.

International control of benzodiazepines under the United Nations Convention on Psychotropic Substances of 1971

Year of scheduling decision	Schedule	Substance name	
1984	IV	Alprazolam	Haloxazolam
		Bromazepam	Ketazolam
		Camazepam	Loprazolam
		Chlordiazepoxide	Lorazepam
		Clobazam	Lormetazepam
		Clonazepam	Medazepam
		Clorazepate	Nimetazepam
		Clotiazepam	Nitrazepam
		Cloxazolam	Nordazepam
		Delorazepam	Oxazepam
		Diazepam	Oxazolam
		Estazolam	Pinazepam
		Ethyl loflazepate	Prazepam
		Fludiazepam	Temazepam
		Flurazepam	Tetrazepam
		Halazepam	Triazolam
1990	IV	Midazolam	
1995	III	Flunitrazepam	
	IV	Brotizolam	
2016	IV	Phenazepam	

Source: UNODC (2017) p. 5.

Recommendations for practice

There are few evidence-based clinical guidelines to support practitioners in the use and management of benzodiazepines among high-risk opioid users. The EMCDDA's Best practice portal (www.emcdda.europa.eu/best-practice) contains seven sets of guidelines as part of general or specific guidelines for managing the use of opioids, benzodiazepines or both.

The Substance Misuse Management Good Practice *Guidance for the use and reduction of misuse of benzodiazepines and other hypnotics and anxiolytics in general practice* in the United Kingdom (Ford and Law, 2014), has a section that focuses on addressing benzodiazepine use by people who use illicit drugs, particularly opioids. Similarly, a recent US Food and Drug Administration Drug Safety Communication (FDA, 2017) provides advice on medication management where there is combined use of prescribed opioids, including opioid substitution medications and benzodiazepines.

Some evidence reviews are also relevant. Soyka (2017) considers the evidence for the management of benzodiazepine withdrawal, including among patients receiving opioid maintenance therapy. A Cochrane review (Darker et al., 2017) considers the evidence concerning the effectiveness of psychosocial interventions for benzodiazepine harmful use, abuse or dependence.

A number of key messages for those addressing benzodiazepine use among opioid users emerge from these different sources:

■ Educate patients about the risks of combined opioid and benzodiazepine use, including overdose and death, both when used as prescribed and when obtained illicitly. Also include education about the risk of concomitant alcohol use.

■ Develop strategies to manage the use of prescribed or illicit benzodiazepines or other CNS depressants when starting opioid substitution treatment. Discuss with patients how they may control and reduce their benzodiazepine use (without the need for a benzodiazepine prescription).

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■ Treat the opioid dependence first, stabilising and optimising opioid maintenance dose.

■ Re-assess patients' benzodiazepine use once they are stable on their opioid prescription because benzodiazepine use may cease or reduce after their opioid maintenance treatment has been optimised.

■ If dependence on benzodiazepines is present, consider a short-term (6 weeks to 6 months), tapering prescription of benzodiazepines (if appropriate consider substitution with a benzodiazepine with longer duration of action before tapering).

■ If a patient is prescribed benzodiazepines or other CNS depressants for anxiety or insomnia, verify the diagnosis and consider other pharmacological options, along with behavioural interventions, for the treatment of these conditions.

■ Monitor for drug use and stop the benzodiazepine prescription if persistent use of illicit drugs, off-prescription use of benzodiazepines or alcohol dependence is present. Consider similar staged detoxification as with other patients dependent on benzodiazepines.

■ Coordinate care to ensure other prescribers are aware of the patient's opioid maintenance treatment and the need to avoid prescription of benzodiazepines and other CNS depressants.

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