Benzodiazepines

Suzanne Nielsen

Abstract Benzodiazepines have been in clinical use since the 1960s. Benzodiazepines act through allosteric modulation of the $GABA_A$ receptor to enhance the activity of GABA, an inhibitory neurotransmitter, resulting in a slowing of neurotransmission and sedative and anxiolytic effects. Initially benzodiazepines were thought to have low dependence liability, though over time there has been increasing evidence of benzodiazepine dependence. Benzodiazepines are commonly used to treat anxiety and insomnia, though increasingly they are considered second line treatments for most indications. Concerns about the effects of benzodiazepines on cognition, falls and their implication in opioid related mortality have emerged. Few pharmacological treatments for benzodiazepine dependence have been shown to be effective with gradual taper the most common treatment strategy for benzodiazepine dependence.

Keyword Benzodiazepine · Misuse · Non-medical use · Dependence

Contents

S. Nielsen (✉)
National Drug and Alcohol Research Centre, UNSW, 22–32 King Street, Randwick, NSW 2031, Australia
e-mail: suzanne.nielsen@unsw.edu.au

S. Nielsen
South East Sydney Local Health District (SESLHD) Drug and Alcohol Services, 591-623 S Dowling St, Surry Hills, NSW 2010, Australia

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1 History of Benzodiazepines

Benzodiazepines have been in clinical use as sedatives/hypnotic drugs since the 1960s, with early benzodiazepines such as chlordiazepoxide and diazepam being used for their improved safety profile over barbiturates (Wick 2013; Morgan 1990). Benzodiazepines were initially promoted as having a low dependence liability in comparison with barbiturates (Morgan 1990). However, by the 1970s prescribing had increased exponentially, and diazepam was the most widely prescribed drug in Europe and the USA (Licata and Rowlett 2008). Benzodiazepine dependence was identified to be a significant clinical concern (Tone 2005) In the 1980s, newer 'benzodiazepine-like' drugs including zolpidem and zopiclone were released, with the intention that they would have lower abuse liability, and shorter onset of action and duration making them ideal for insomnia. However, these newer drugs are also associated with abuse and dependence (Victorri-Vigneau et al. 2014).

2 Pharmacology and Clinical Effects

Benzodiazepines act through allosteric modulation of the $GABA_A$ receptor, increasing the affinity of the receptor for GABA leading to increased subsequent chloride conductance (Campo-Soria et al. 2006). Through their action at the $GABA_A$ receptor, benzodiazepines and benzodiazepine-like drugs enhance the activity of GABA, an inhibitory neurotransmitter, resulting in a slowing of neurotransmission and sedative and anxiolytic effects.

Most therapeutic uses of benzodiazepines are related to their anxiolytic, muscle relaxant and sleep-promoting effects. The effects of therapeutic doses of benzodiazepines on physiological parameters including respiration have been examined in non-opioid-maintained subjects. Administration of therapeutic doses of diazepam to healthy controls has been demonstrated to induce significant impairment of mental alertness and cognitive performance without producing significant effects on respiration (Mak et al. 1993; Bond 1993). Benzodiazepine has considerable effects on cognition, with low doses being sufficient to significantly impair driving ability (Verster et al. 2002). Benzodiazepines have been demonstrated to have an effect on memory, specifically newly learned material following benzodiazepine

Table 1 Benzodiazepine half-lives and dose equivalence

Benzodiazepine with examples of common brand names	Half-life	Dose equivalent to diazepam 5 mg (Therapeutic guidelines limited 2015) (mg)
Alprazolam: Kalma®, Xanax®	Short–intermediate	0.5
Bromazepam: Lexotan®	Short–intermediate	3
Clobazam: Frisium®	Intermediate	10
Clonazepam: Rivotri®, Paxam®	Intermediate	0.25
Diazepam: Antenex®, Ducene®, Valium®	Long	5
Flunitrazepam: Hypnodorm®, Rohypnol®	Intermediate	0.5
Lorazepam: Ativan®	Short–intermediate	1
Nitrazepam: Alodorm®, Mogadon®	Intermediate	5
Oxazepam: Alepam®, Murelax®, Serepax®	Short	15
Temazepam: Euhypnos®, Normison®, Temaze®	Short	10

administration (Curran 1986; Verster and Volkerts 2004). These amnestic effects can be desirable during surgical procedure.

Benzodiazepines are often classified as short, medium (or intermediate), or long acting depending on their duration of action and the time it takes for them to be cleared from the body. For example, midazolam is a short-acting benzodiazepine with an onset of 2–10 min depending on the route of administration and short duration of action lasting up to a few hours (Therapeutic Guidelines Limited 2015). In contrast, diazepam is a long-acting benzodiazepine with a half-life of 24–36 h (see Table 1).

3 Abuse and Dependence Liability

Midazolam, triazolam, flunitrazepam, and diazepam have been shown to demonstrate dose-dependent reinforcing effects in animals (Bai et al. 2011; Fischer and Rowlett 2011; Gomez et al. 2002; Gerak et al. 2001) abuse potential in humans (Carter 2007).

Certain characteristics are associated with greater self-administration of benzodiazepines under experimental conditions. Amongst healthy adolescents, benzodiazepine effects were found to vary as a function of sensation seeking, where those that scored higher on sensation-seeking scales reported greater sedative effects of

diazepam, while low sensation seekers reported lower ratings measures indicative of abuse potential (Kelly et al. 2009). Diazepam has also found to be more reinforcing for people with social anxiety, and under experimental conditions that create anxiety (Helmus et al. 2005), and more reinforcing than buspirone in moderate alcohol consumers (Evans et al. 1996). Similarly, levels of alprazolam self-administration under double-blind conditions were positively associated with anxiety levels in patients with anxiety (Oswald et al. 1999). In contrast, amongst cannabis users, triazolam was not shown to function as a reinforcer at the doses examined, although significant effects were seen on participants' ratings of wanting to take the drug again and willingness to pay for the drug (Lile et al. 2010), which are generally associated with abuse liability. Taken together, these studies suggest that differences in characteristics and substance use may influence the likelihood of benzodiazepine use.

Despite their ability to maintain self-administration, benzodiazepines tend to have lower abuse liability compared with other drug classes such as opioids, barbiturates, cocaine, and GHB (Licata and Rowlett 2008; Carter et al. 2006). Further, drugs with shorter half-lives and shorter onset of action may have greater reinforcing effects (Licata and Rowlett 2008). Small studies suggest, for example, that alprazolam may have greater abuse liability than diazepam (Apelt et al. 1990), though few large rigorous study designs have examined this question. Long-term use can lead to neuroadaptation and physical dependence, further increasing the likelihood of abuse. Despite their lower propensity for self-administration compared to other drugs, misuse and the development of dependence are commonly reported amongst patient populations, either alone or in combination with other drugs. Dependence to benzodiazepines can begin to develop in as little as a week (Licata and Rowlett 2008), though not all patients develop dependence to benzodiazepines with long-term use (Woods et al. 1992).

Benzodiazepine dependence commonly presents with other drug dependence; benzodiazepine dependence as the primary drug of concern typically accounts for a very small proportion of treatment admission (e.g. less than one per cent in the USA) (Substance Abuse and Mental Health Services Administration 2011). Despite low numbers of treatment admissions, a large number of emergency data visits are now attributed to benzodiazepine use, with the presence of benzodiazepine use predicting a more serious outcome from an emergency department visit when present alone or with other drugs (Substance Abuse and Mental Health Services Administration 2014).

4 Indications for Benzodiazepines

One of the challenges with examining 'misuse' and 'abuse' of benzodiazepines is the large overlap between clinical use, self-administration for therapeutic purposes, and non-medical use. Non-prescribed use is commonly reported to be for reasons that appear therapeutic.

There are a range of reasons why benzodiazepines may be prescribed to patients, though benzodiazepines are rarely recommended as first-line treatments. Non-drug treatments and other medications such as antidepressants are considered first-line treatments for chronic anxiety or insomnia, with benzodiazepines reserved for second-line use when patients are unable to tolerate first-line medications, or after non-drug treatments have failed (Dellemijn and Fields 1994). Although benzodiazepines are effective when used acutely for generalized anxiety or panic disorders, they are not listed in clinical guidelines as first-line treatments for these conditions. For example, Australian guidelines indicate short-term use, or only where antidepressants are not tolerated (Therapeutic Guidelines Limited 2015; Joint Formulary Committee 2013). A recent international review of current guidelines report described the current role of benzodiazepines in generalized anxiety disorder to be largely limited to a second-line treatment for the acute phase, either until antidepressants or psychological treatments can be established, with caution using in specific populations including young people, the elderly, and those with a history of substance use disorder (Short- and Long-Term Use of Benzodiazepines in Patients with Generalized Anxiety Disorder 2014).

Benzodiazepines are also commonly used amongst those prescribed opioids for chronic pain (Nielsen et al. 2015). One review, conducted two decades ago, identified a limited role for benzodiazepines in acute pain in only a small number of conditions with little evidence from controlled studies to support their general use in chronic pain (Dellemijn and Fields 1994). Despite this, around one in three chronic pain patients continue to be prescribed benzodiazepines (Nielsen et al. 2015).

5 Prevalence of Use and Misuse

In the USA, national household surveys reveal that around 4 % of respondents reported tranquilizer use and 6 % reported using sleeping pills or other sedative use (Brower et al. 2011). Similar estimates from the UK report 3 % of the population use benzodiazepines (Ohayon et al. 1998). In Australia, over 5 million prescriptions for benzodiazepines are subsidized by the government each year (Medicare Australia 2011), accounting for approximately 4–5 % of all prescriptions written by general practitioners (Johnson et al. 2007). Many more benzodiazepines are supplied as private prescriptions that are not captured in any routine monitoring systems. Although there has been some reduction in benzodiazepine use (Islam et al. 2014; Tsimtsiou et al. 2009), they continue to be commonly prescribed, despite few indications for their use existing.

In some clinical populations, benzodiazepine use far exceeds that seen in the general population. For example, patients taking long-term opioids, both for chronic pain and in the context of treatment for illicit opioid use, have much higher rates of benzodiazepine use than the general populations (Nielsen et al. 2015; Ross and Darke 2000). Preclinical studies suggest that benzodiazepine may modulate the

rewarding effects of heroin (Walker and Ettenberg 2001). Consistent with this, human laboratory-based studies where opioids and benzodiazepines are coadministered indicate that there may be additive subjective effects of opioids and benzodiazepines, with benzodiazepine administration potentially increasing the subjective opioid effects of methadone (Preston et al. 1984). Alcohol-dependent populations may also have higher rates of benzodiazepine use than the general public (Ciraulo et al. 1988), with benzodiazepines being commonly used to treat alcohol withdrawal. Alcohol-dependent people also have high rates of anxiety disorders which may increase susceptibility to benzodiazepine misuse (Helmus et al. 2005). High rates of benzodiazepine use have been reported amongst nursing home populations, which is concerning in light of increased fall risk that has been attributed to benzodiazepines (de Vries et al. 2013). One of the complicating characteristics of chronic benzodiazepine use is that when long-term use leads to dependence, the withdrawal symptoms (such as insomnia and anxiety) are similar to the initial symptoms the drugs are used to treat (Charney et al. 2006). This can result in patients perceiving that they are still treating their incident condition rather than having developed dependence.

Limited detailed research examines benzodiazepine use at a population level. A recent US study on benzodiazepine use amongst adolescents used data from the National Survey of Drug Use and Health (NSDUH) to examine characteristics and theoretical risk factors associated with benzodiazepine use amongst adolescents (Rigg and Ford 2014). The authors found that being female, being older, and viewing substances use as less risky were associated with lifetime benzodiazepine misuse. Those with peers with more lenient attitudes towards substance use and who were under more strain (based on an index of negative life events such as arguments with parents or low grades in school) were also associated with increased risk of misuse. Other substances use was also associated with increased risk, consistent with previous research that generally finds benzodiazepines are used in a context of polydrug use.

In a study of high school seniors (modal age of 18 years), approximately 5 % report medical use and 8 % report non-medical use of benzodiazepines (McCabe and West 2014). Correlates of non-medical use were similar in these two studies with being female and white being associated with increased non-medical use in both studies, along with use of other substances, including non-medical use of other types of pharmaceuticals.

Most research on benzodiazepine use at a population level comes from countries such as the UK and the USA, though misuse and dependence not limited to these countries. For example, in France, benzodiazepines are thought to be misused more often than most opioid analgesics, excluding morphine (Pauly et al. 2012). A household survey in Thailand identified around 4 % of the population were current benzodiazepine users, and 57 % of those that were using benzodiazepines reported misuse of them (Puangkot et al. 2011). Other studies identify considerable concerns, with emerging awareness of benzodiazepine-related problems reported in countries including Albania, India, and Lebanon (Kellici et al. 2013; Nattala et al. 2014; Naja et al. 2000).

5.1 Adverse Effects from Benzodiazepine Use

5.1.1 Dependence

Iatrogenic dependence is common with benzodiazepines due to the dependence liability of this class of drugs (Denis et al. 2006) and may occur following therapeutic use of benzodiazepines for a range of psychiatric conditions including anxiety and panic disorder as well as for the treatment of insomnia.

5.1.2 Aggression

Increased hostility, anger, and aggression have been reported following benzodiazepine administration in preclinical (Miczek et al. 1993) and human studies (DiMascio 1970). More than fifty years ago, reports of aggression were recorded with chlordiazepoxide (Boyle and Tobin 1961). Other early studies described rage attacks and 'egodystonic hatefulness' in association with diazepam use (Feldman 1962). Other unwanted benzodiazepine effects include disinhibition, paradoxical hostility, and anterograde amnesia (Daderman and Lidberg 1999; Dobbin 2001; Rall 1992; Bonn and Bonn 1998). Benzodiazepine use has been linked to criminal behaviour and in at-risk populations may contribute to further harms for both the user and the community (Jones et al. 2011). The finding of a dose-related effect of flunitrazepam on risky decision-making may partially explain these findings (Lane et al. 2007). Paradoxical hostility is an unexpected side effect of benzodiazepines, given their known ability to generally cause sedation and reduce anxiety. Daderman and Lidberg (1999) studied five forensic patients that demonstrated paradoxical reactions to flunitrazepam when it was used in combination with alcohol and other drugs (Daderman and Lidberg 1999). The reactions included hostility and anterograde amnesia, which were noted to be in contrast to patients based usual psychological characteristics. Similar paradoxical responses have been reported with benzodiazepines, including alprazolam and diazepam (French 1989; Rudorfer et al. 1989).

The mechanisms of paradoxical reactions are yet to be fully elucidated (Mancuso et al. 2004; Robin and Trieger 2002). Paradoxical reactions are thought to be more common amongst certain group of patients, including children, and those that use substances including alcohol. A possible role of genetics and serotonergic mechanism have been suggested. Common treatment approaches include administration of flumazenil, a benzodiazepine antagonist.

5.1.3 Dementia and Other Cognitive Effects

Long-term benzodiazepine use can result in cognitive impairment across numerous cognitive domains (Barker et al. 2004). A review of benzodiazepine use and dementia identified that 9 out of 10 studies examined identified an association, with

increased risk of dementia following benzodiazepine use. When only the high-quality studies were examined, the risk was found to be increased by a factor of 1.24–2.30. The greatest risk was with higher doses, longer term use, and long half-life benzodiazepines. Use of longer than three years was associated with the greatest risk that did not disappear on cessation of benzodiazepines (Billioti de Gage et al. 2015).

5.1.4 Mortality

Clearly, the most concerning adverse effect associated with benzodiazepines is mortality. Benzodiazepine use is commonly implicated in opioid deaths, including heroin, methadone, and other prescription opioids (Zador and Sunjic 2000; Gerostamoulos et al. 2001; Caplehorn and Drummer 2002; Ernst et al. 2002; Jann et al. 2014). Similarly, benzodiazepine use has been implicated as a significant risk factor for non-fatal heroin overdose (Gutierrez-Cebollada et al. 1994; Neale 2000; Dietze et al. 2005).

Concerns with mortality exist in therapeutic as well as non-medical use. For example, a Swedish study of 2249 patients starting long-term oxygen therapy for COPD between 2005 and 2009 found that benzodiazepines were dose dependently associated with increased mortality (Ekstrom et al. 2014).

5.1.5 Falls

An association with benzodiazepine use and falls has been established. For example, an Irish cohort study of 6666 adults aged 50 years or more found that benzodiazepines were associated with a greater number of falls (Richardson et al. 2015). Further studies have tried to identify which benzodiazepine characteristics are associated with more falls; however, findings have been mixed. One prospective observational study found an association with only short-acting benzodiazepines and falls, with non-significant associations with long-acting benzodiazepines (de Vries et al. 2013). A separate matched case-control study also identified an association with shorter elimination half-life benzodiazepines, but found recent dose escalation and total dose of benzodiazepines to be more important contributors to falls (Herings et al. 1995).

6 The Spectrum of Benzodiazepine Use: From Therapeutic to Non-medical Use and Dependence

Optimal use of benzodiazepines is outlined in clinical guidelines (Practitioners RRACoG 2000). General feature of optimal use includes the following:

- Avoiding prescribing in high-risk groups (e.g. people with substance use disorder);
- Advising patients of the risk of dependence;
- Having only one prescriber providing prescriptions;
- Regular review;
- Use of non-drug management for conditions such as anxiety and insomnia; and
- Using the lowest dose for the shortest period possible (no longer than 2–4 weeks).

Where dependence has been established, with the patients consent, it is recommended to transfer doses to one long-acting benzodiazepine and gradually reduce (often over several months).

Unfortunately, much benzodiazepine use occurs outside these parameters with benzodiazepines commonly being used for long periods of time in the absence of other strategies to treat the primary indication. Further complicating this clinical picture is the similarity between benzodiazepine withdrawal symptoms (e.g. agitation, anxiety, insomnia, and panic attacks) and the indications they are initially commenced for.

Box 1. A case of escalating benzodiazepine use Rachel was a final-year nursing student under a lot of financial stress and approaching her examinations. She was finding it increasingly difficult to sleep at night and went to see her doctor for help. She received an initial script for temazepam 10 mg (25 tablets) and was advised just to take it for a few days. She found the temazepam helped and after a few days attempted to sleep again without them. Her insomnia was still a problem, and Rachel decided to keep taking them just until she was finished with her examinations. Three weeks later, in the middle of her examinations, she ran out of temazepam and had 'the worst night of sleep ever'. She returned for another script of temazepam just to get her through the last few days of examinations. She ended up finishing the second bottle, and by this stage, she had been taking benzodiazepines to sleep almost every day for two months. She was finding that they were not working as well, and she needed a higher dose to get the same effect. After a few months, if she went without them, in addition to having a lot of trouble sleeping, she would experience anxiety and panic attacks during the day. After pleading with her doctor for something to help her sleep and to help with the panic attacks, she was prescribed a higher dose of temazepam and alprazolam for panic attacks during the day. After continuing on these medications, a number of months Rachel decided to seek help for her panic attacks as they were getting worse. She disclosed at this time that her benzodiazepine use was now much higher than intended and that she was seeing multiple doctors to make sure she did not run out. With the help of her family doctor and a specialist in addiction medicine, she was eventually converted onto a long-acting benzodiazepine (diazepam) started on a withdrawal

programme, where she reduced over 6 months and eventually stopped all benzodiazepines. She worked with a psychologist to learn cognitive behavioural techniques to help with her sleep and panic attacks. She was still experiencing symptoms of anxiety and insomnia several months after ceasing benzodiazepines.

Some of the challenges in addressing benzodiazepine 'misuse' is that their use is often in the context of self-medication of insomnia and other psychological disturbances [e.g. (Gelkopf et al. 1999; Perera et al. 1987)]. In other cases, benzodiazepine use occurs in the context of polydrug use, for example with opioids to either increase opioid effects, for example, in times of lower purity illicit opioids or where greater euphoric effects are desired [e.g. (Darke et al. 1995; Iguchi et al. 1993)].

A large study of 1048 patients that had received benzodiazepines on prescription for at least one month examined characteristics and risk factors associated with dependence (de las Cuevas et al. 2003). Unsurprisingly, increasing dose and duration was correlated with the rate of developing dependence. The third factor associated with dependence was coprescription of an antidepressant, potentially acting as a proxy for poorer psychological health, though this was not significant after controlling for dose and duration of benzodiazepines.

Amongst older adults (65 years and older), prescribed benzodiazepines for at least three months, around three in ten, were identified to be dependent (Yen et al. 2014). Use of zolpidem (as opposed to estazolam or flunitrazepam) and current depression were associated with misuse (Yen et al. 2014). A separate study of older adults in Quebec identified that while one in ten met diagnostic criteria for substance dependence, almost half identified as being dependent and a third agreed it would be good to stop taking benzodiazepines (Voyer et al. 2010). A third study examined outcomes of benzodiazepine prescribing to older adults who were newly initiated onto benzodiazepines (Simon and Ludman 2006). This study identified that insomnia (42 %) and anxiety (36 %) were the most common reasons for benzodiazepine prescription and that 30 % of those initiated on benzodiazepines were taking them daily after two months.

Recreational use of benzodiazepines is not uncommon. Amongst a small sample ($n = 15$) of college students, the most common reasons for misuse were 'to get high or party' (33 %), or to relax or 'zone out' (27 %) (Stone and Merlo 2011).

A recent survey in the UK identified that around three out of ten people who have taken benzodiazepines had 'misused' them. Some of the reasons most commonly reported for misuse were largely similar to their therapeutic indications such as sleep (66 %) and help cope with stress (37 %), or for recreational reasons such as 'to get high' (31 %) or for social reasons (24 %) (Kapil et al. 2014). One in ten reported that they misused them because they felt they were safer than street/illegal drugs (Kapil et al. 2014).

7 Benzodiazepines and Polydrug Use

Benzodiazepine use amongst methadone patients has also been found to be common in many settings, with recent use reported by 44–70 % and lifetime use reported by up to 100 % amongst different methadone treatment samples (Gelkopf et al. 1999; Iguchi et al. 1993; Stitzer et al. 1981; Barnas et al. 1992; Hartog and Tusel 1987; Chen et al. 2011). Similarly, benzodiazepine use has been reported to be common amongst buprenorphine treatment participants (Nielsen et al. 2007).

In- and out-of-treatment samples of people who use heroin commonly report benzodiazepine use; around 25 % of heroin users are believed to be benzodiazepine dependent (Ross and Darke 2000; Darke et al. 1992). Amongst Australian heroin-dependent treatment entrants, just over half (52 %) reported using benzodiazepines in the previous month (Ross et al. 2005).

Different characteristics have been reported amongst patients seeking treatment for benzodiazepine abuse or dependence. One study of $n = 176$ patients referred for assessment and treatment of their benzodiazepine abuse and/or dependence found at least two subgroups treatment seeking of benzodiazepine users (Busto et al. 1986). The first was a group using only benzodiazepines in lower diazepam equivalent doses (approximately 15 mg daily), while a second group was using multiple substances and higher benzodiazepine doses, (approximately 40 mg daily of diazepam equivalents) with more dose escalation. A larger study of 2440 people receiving long-term benzodiazepines had similar findings: most recipients of a long-term benzodiazepine script did not increase their dose and remained on a low dose (around 10 mg daily of diazepam equivalents), though a small subset (1.6 %) did increase their dose (Soumerai et al. 2003). This subgroup were characterized by concurrent antidepressant use, use of multiple pharmacies, and younger age.

8 Perceptions of Benzodiazepine Use

Amongst people who use drugs, benzodiazepine use is often perceived to be less of a concern than other drugs. Amongst parents of young children participating in opioid treatment, benzodiazepine use and benzodiazepine dependence were relatively normalized, with reducing use reported to be less of a priority than addressing opioid use (Chandler et al. 2014). While opioid use was perceived as stigmatizing, benzodiazepine use was perceived to be a helpful part of their 'normal' life (Chandler et al. 2014). Reasons reported for use included insomnia and helping with nerves and mood with few adverse effects noted. A separate qualitative study of polydrug users reported similarly that benzodiazepines were perceived to be 'less risky' than illicit drugs such as heroin due to being of a known quantity (Fountain et al. 1999).

Patient perceptions often also suggest benzodiazepine use is in the context of self-medication. A qualitative study of opioid treatment patients in Virginia

reported that benzodiazepines are often used in combination with opioids for anxiety, commonly referring to them as 'nerve pills' (Redican et al. 2012).

Perceptions of older women, a population who are overrepresented amongst benzodiazepine-dependent people (Voyer et al. 2010), suggested that amongst some there was some confusion of what dependence is, drawing parallels with needing medication for diabetes and blood pressure medications, and drawing distinctions between physical dependence and 'addiction' (noting the latter as a concern and denying being 'addicted') (Canham et al. 2014). Participants also reported that use was not problematic as they had been 'told to' take their medications by a doctor, reserving the concept of 'addiction' for illicit drugs.

A study of young to middle-aged people (n = 212) taking long-term benzodiazepines found half (49.7 %) met diagnostic criteria for benzodiazepine dependence, though only a small group of these patients (n = 29) reported acquiring them in ways other than sanctioned medical supply (Guerlais et al. 2015). This study identified two clinical profiles of benzodiazepine-dependent people, one with tolerance (and increasing doses) and long-term use, and a second with concern about use and somatic consequences of benzodiazepine use. In this study, the greater benzodiazepine use was associated with substance use and psychiatric disorders.

9 Responses to Benzodiazepine Misuse and Dependence

Given the considerable harms associated with benzodiazepine use, there are relatively few widely used clinical responses.

Prescription monitoring is commonly proposed to address pharmaceutical misuse. Where prescription monitoring has been implemented, significant reductions in inappropriate benzodiazepine use have been reported (Gomes et al. 2014). It should be noted that, as a result of benzodiazepines being classed in different levels of regulation than strong prescription opioids, they are sometimes excluded from prescription drug monitoring programmes (Nielsen 2014).

Lower levels of reimbursement have also been associated with reduced benzodiazepine use (Hoebert et al. 2012).

Strategies to monitor and respond to benzodiazepine use in clinical care include routine urine drug screen, to detect non-prescribed use (Gudin et al. 2013). Where low doses of benzodiazepines are prescribed, the use of benzodiazepines such as clonazepam and clobazam that do not have active metabolites can help aid in the detection of unsanctioned benzodiazepine use (Lintzeris and Nielsen 2010).

Two systematic reviews address strategies for reducing the use of benzodiazepines. A Cochrane review that examined data from with 458 subjects across eight randomized controlled trials (RCTs) (Denis et al. 2006) identified supported for transferring patients to a long-acting benzodiazepines, stabilization preceding a gradual taper over weeks to months, and found a limited role for adjuvant medication therapy (including beta blockers, some tricyclic antidepressants such as

dothiepin, buspirone, and progesterone). Carbamazepine showed modest effects in reducing benzodiazepine withdrawal symptoms (Schweizer et al. 1991).

A second review (Parr et al. 2009) identified several RCTs, most conducted one to two decades ago, using adjuvant medications. Results included inconsistent findings with paroxetine and positive findings in one study for trazodone and sodium valproate. It should be noted that most controlled studies in this area were conducted 1–2 decades ago, and the role of newer medications in assisting benzodiazepines withdrawal has not yet been explored in controlled trials. Promising anecdotal and case reports regarding the role of new-generation antidepressants (e.g. mirtazapine), new-generation antipsychotic medications (e.g. olanzapine, aripiprazole), medications that impact upon GABA receptor system (e.g. gabapentin), and benzodiazepine receptor antagonists (e.g. flumazenil) warrant further research.

Parr et al. (2009) also examined the role of psychosocial interventions in addition to gradual dose reduction (Parr et al. 2009). Common features of these interventions included relaxation training, symptom management, and cognitive behavioural techniques. Findings were variable, with positive outcomes from psychosocial interventions in four of the eight studies.

While research identified approaches to reduce benzodiazepine doses, many patients appear unable to maintain long-term abstinence from benzodiazepine dependence. For example, benzodiazepine in a general practice setting with older adults (mean age 63 years) found that despite using relatively low doses of benzodiazepines at baseline (mean diazepam equivalent dose of 8.4 mg), most (88 %) had recommenced benzodiazepine use within 15 months of benzodiazepine reduction (Oude Voshaar et al. 2006). The difficulties experienced in tapering patients off benzodiazepines highlight the importance of strategies that prevent the development of dependence, specifically, addressing inappropriate prescribing that leads to dependence. This is in addition to identifying effective medications to assist in withdrawal for those that do develop dependence.

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