Opiate Abuse: A Review of the Combined Use of Opioids and Benzodiazepines

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Abstract: This article reviews studies investigating the pharmacological interactions and epidemiology of combined opioid and benzodiazepine (BZD) use. A search of English language publications from 2015 to 2023 was conducted using PubMed and PsycINFO®. Our search identified approximately 10 articles suitable for inclusion in this paper with the search characteristic of combined opiate and BZD use. Despite numerous reports indicating that opioid and BZD abuse is ubiquitous worldwide, the reasons for abuse of these drugs are not entirely clear. While opioid users may use BZDs therapeutically to treat anxiety, mania or insomnia, the data reviewed in this paper suggest that BZD use is primarily recreational. For example, co-users reported seeking BZD prescriptions to increase opioid intoxication or 'sobriety', and using doses that exceeded the therapeutic range. As few clinical studies have investigated the pharmacological interactions and abuse potential of their combined use, this hypothesis has not been extensively evaluated in a clinical setting. Therefore, our analysis encourages further systematic investigation of BZD abuse among opioid users. Co-abuse of BZDs and opioids is substantial and has negative consequences for general health, overdose mortality and treatment outcomes. Clinicians should address this important and under-recognised issue with more cautious prescribing practices and increased vigilance for patterns of misuse.

1 INTRODUCTION

It is estimated that around 61 million people worldwide will use opioids in 2020. Nonmedical use of opioids is reported in all regions and almost all countries. Prevalence rates are highest in North America, South-West Asia, Oceania and South Asia (UNODC, 2022). The United States and many other Western countries are experiencing an increase in the use and abuse not only of opioids but also of other drugs that affect the activity of the central nervous system. In particular, the use of benzodiazepines, the most commonly prescribed tranquillisers, has risen sharply over the past decade, with an estimated 3% of the general population receiving long-term prescriptions for these drugs. Benzodiazepines are approved for a wide range of conditions, particularly anxiety and sleep disorders. In addition, benzodiazepines are generally considered to be of good overall safety, but like opioids, benzodiazepines have the potential for dependence and toxicity when used for long periods and at high doses.

Unbeknownst to many patients and prescribers, benzodiazepines are far more dangerous when prescribed in combination with opioids than when taken separately. Benzodiazepines and opioids suppress breathing, increasing the risk of potentially fatal apnoea. Accumulating data show that drugs such as benzodiazepines contribute significantly to opioid-related deaths. The US Centers for Disease Control and Prevention (CDC) has recognised this threat and is urging doctors to avoid prescribing opioids and benzodiazepines together whenever possible. In addition, the US Food and Drug Administration (FDA) has placed a black box label on the combination drug, highlighting the dangers of concurrent prescribing. Nevertheless, concomitant prescribing is still a common practice among doctors. However, it is known that the risk of harm (or benefit) from using strong opioids or benzodiazepines depends on the context. For example, a combination of drugs may be prescribed to treat anxiety and chronic pain. This review summarises the currently available evidence on the risk of serious harm to patients when opioids and benzodiazepines are used together and categorises the results according to different clinical and outpatient conditions.

Benzodiazepines and opioids are among the most

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commonly abused classes of psychoactive drugs in the world (Grytten, 1998; Joranson et al., 2000; Substance Abuse and Mental Health Services Administration, 2008). Not surprisingly, the concurrent use of these two classes of drugs has attracted the attention of researchers and clinicians since the 1970s (Kleber and Gold, 1978). The aim of this review is to gain a better understanding of the motivations for and consequences of their concomitant use. Using PubMed and PsycINFO, we searched for English-language articles on this topic published between 1970 and 2012.

Different combinations of the following search terms were used: opioid, benzodiazepine, heroin, methadone, polydrug abuse, concomitant use, co-administration, prescription opioid, midazolam, valium, diazepam, alprazolam, flunitrazepam, pharmacological interactions and epidemiology. Using this method, we identified more than 5,000 publications. After removal of duplicates, titles and abstracts were checked for relevance by the authors. Data from approximately 10 articles were included in this manuscript. This review and synthesis of this literature focuses on clinical studies investigating the pharmacological interactions between opioids and BZDs and the epidemiology of their co-abuse. Clinical research is the focus of this paper. At times, however, preclinical data are used to complement these findings and to support the authors' conjectures about the motivations and risks underlying the co-use of opioids and BZDs.

This review begins with a brief overview of the abuse of each drug alone, followed by a review of the clinical literature investigating the pharmacological interactions between opioids and BZDs. Finally, we review reports on the prevalence and consequences of BZD and opioid co-abuse. It is hoped that this review will lead to a better understanding of: how these drugs interact pharmacologically; which populations abuse these two drugs and why; the prevalence of their co-abuse; and the clinical implications of this behaviour.

2 METHODS

This research was conducted based on a literature review approach, which was obtained from 20 international and national papers that included discussions on data visualisation and digital field data retrieval, which were then made into review papers through the 20 journals, in order to provide additional knowledge that hopefully can add new insights, made in such a way as to produce new scientific work in the form of narrative reviews. Our search identified approximately 20 articles suitable for inclusion in this paper, with the search characteristic of combined opiate and BZD use. Despite numerous reports indicating that opioid and BZD abuse is ubiquitous worldwide, the reasons for abuse of these drugs are not entirely clear. While opioid users may use BZDs therapeutically to treat anxiety, mania or insomnia, the data reviewed in this paper suggest that BZD use is primarily recreational.

3 RESULTS AND DISCUSSION

20 Literature on the misuse or deliberate abuse of opioids and tranquillisers, mostly with benzodiazepines. In addition to opiate contraindications with benzodiazepines, there are also opiate contraindications with gabapentin, cocaine and alcohol. Data were obtained from retrospective cohort analyses and post-mortem analyses of deceased patients. All data showed death or serious adverse effects with the use of benzodiazepines and opiates. In general, most data showed that the use of opiates with benzodiazepines or other centrally acting drugs increased over the years and that the combination of these drugs increased the risk of death.

Abrahamson's study found that concomitant use of opioids and benzodiazepines may increase non-overdose mortality. In addition, the concurrent use of opioids and pregabalin also increases the risk of death. Meanwhile, Visconti's research shows that using opiates with alcohol may cause very few deaths. Patients on opioid replacement therapy with buprenorphine or methadone. The data from this study showed that benzodiazepines were involved in most deaths. Interestingly, patients on methadone replacement therapy may have a higher risk of death and adverse effects of severe respiratory illness when using a benzodiazepine concomitantly than patients on buprenorphine replacement therapy. Although the use of benzodiazepine with opioids (methadone or buprenorphine) may cause a risk of death or acute respiratory side effects, benzodiazepine is particularly needed in PTRM patients. benzodiazepine to treat anxiety in PTRM patients. Use is controlled with an individual dose.

4 A BRIEF OVERVIEW OF OPIOID ABUSE

The opioid class of drugs includes natural opiates

(e.g., morphine, codeine, salvia divinorum), semi-synthetic opioids (e.g., heroin, oxycodone, hydromorphone, hydrocodone, salvanorin A), and synthetic opioids (e.g., methadone, buprenorphine, and fentanyl; National Institutes on Drug Abuse/U.S. Dept. of Health and Human Services, 2009). Opioids have multiple effects: they alter body temperature, cause sedation, depress respiration, induce eating, decrease gastrointestinal transit, affect urine output, and produce either euphoria or dysphoria (Broekkamp et al., 1984; Teasdale et al., 1981; Wise, 1989). These effects are primarily produced by actions at the three opioid receptor subtypes: μ, κ and δ. Of the subtypes, the μ opioid receptor is the best known and most studied. Activation of the G protein-coupled μ receptor leads to acute changes in neuronal excitability. It is the agonist action of opioids on μ receptors that is thought to underlie their ability to relieve pain, suppress cough and relieve diarrhoea. Important indicators of abuse potential are the extent to which a drug produces reinforcing effects and positive subjective effects. These are typically assessed in humans using subjective questionnaires and drug self-administration paradigms (Comer et al., 2008a; Haney and Spealman, 2008). Preclinically, self-administration and conditioned place preference (CPP) paradigms are commonly used to study the reinforcing and rewarding effects of drugs (Epstein et al., 2006; Haney and Spealman, 2008; Willner, 1997). The abuse potential of μ-opioid receptor agonists has been extensively demonstrated in rodents, non-human primates and humans (for reviews see Kieffer and Gavériaux-Ruff, 2002; Preston and Jasinki, 1991 and Trigo et al., 2010). This research indicates that heroin has considerable potential for abuse, and epidemiologically its abuse is a significant public health problem (Comer et al., 2008b; European Monitoring Centre for Drug and Alcohol Dependence, 2010; Jasinksi and Preston, 1986).

Worldwide, an estimated 9.2 million people are regular heroin users, with an estimated 1.2 million active heroin users in the USA (0.6 % of the population aged 15-64; Bammer, 1999; Epstein, 1997; United Nations Drug Control Programme (UNDCP), 2001; United Nations Office for Drug Control, Crime Prevention (UNODC), 2002; 2010). In 2009, about 180 000 persons aged 12 years or older used heroin for the first time. In the same year, 507 000 people sought treatment for heroin use, and nearly 20 % (> 200 000) of all emergency department visits for illicit drugs included reports of adverse reactions to heroin or other heroin-related consequences (Substance Abuse and Mental Health Services Administration (SAMSHA), 2010).

Like heroin, μ-receptor-selective prescription opioids, including morphine, hydrocodone, hydromorphone, fentanyl, buprenorphine and oxycodone, have demonstrated significant abuse liability in humans (Comer et al., 2008b; Middleton et al., 2011; Walsh et al., 2008; Zacny and Lichtor, 2008). Abuse of buprenorphine is particularly prevalent in Europe, where buprenorphine treatment was widely available several years before its use in the US (Auriacombe et al., 2001; Carrieri et al., 2006). Recreational use of prescription opioid analgesics has risen sharply in the United States over the past two decades. Data from epidemiological surveys, treatment admissions and emergency department records also indicate an increasing prevalence of prescription opioid misuse (Cicero, 2005; Gilson et al., 2004; Substance Abuse and Mental Health Services Administration, 2010). In some parts of the US, unintentional drug poisoning deaths from opioid analgesics have increased by 20% in recent years (2005-2009: New York City Department of Health and Mental Hygiene, 2011). The 2009 National Survey on Drug Use and Health (NSDUH) found that the number of new initiates for non-medical use of opioid analgesics (2.2 million) was second only to marijuana (2.4 million) and surpassed well-known drugs of abuse such as cocaine (0.6 million), methamphetamine (0.15 million) and ecstasy (1.1 million) (Substance Abuse and Mental Health Services Administration, 2010). Recent estimates put the prevalence of non-medical use of prescription opioids in the past year at about 5.3 million, with up to 13% of these individuals meeting DSM-IV criteria for abuse or dependence (Becker et al., 2008; Substance Abuse and Mental Health Services Administration, 2009). Prescription opioids are often abused in combination with benzodiazepine-type drugs. Together, opioids and BZDs accounted for the majority of ED visits for non-medical use of psychotherapeutics (Substance Abuse and Mental Health Services Administration, 2011a).

5 BRIEF OVERVIEW ON BENZODIAZEPINE ABUSE

Benzodiazepines are among the most widely prescribed psychotropic drugs in the world (Coach, 1990). These drugs, whose core chemical structure is the fusion of a benzene and a diazepine ring, act as positive allosteric modulators of the GABA receptor complex.

Benzodiazepines act to enhance the effects of

GABA by increasing chloride (Cl-) flux and the rate of channel opening. These drugs are a commonly used and effective treatment for anxiety disorders and an adjunctive treatment in several psychiatric and neurological conditions (Bateson, 2004; Campo-Soria et al, 2006; Doherty, 1991; Low et al, 2000; McKernan et al, 2000; Saunder and Ho, 1990). Activation of the GABA/barbiturate/steroid receptor sites is thought to produce the muscle relaxant effects of benzodiazepines (Bateson, 2004; Campo-Soria et al., 2006; Saunder and Ho, 1990), and activation of the various α GABA subunits has been implicated in their sedative and anxiolytic effects (Low et al., 2000; McKernan et al., 2000). Unlike some of their other effects, the reinforcing effects of BZDs are not easily attributed to a single receptor subtype (Licata and Rowlett, 2008). A number of BZDs have been shown to act as reinforcers in rodents and non-human primates, including: diazepam, chlordiazepoxide, flurazepam, lorazepam, medazepam and midazolam (Bergman and Johanson, 1985; Findley et al, 1972; Gotestam, 1973; Griffiths et al, 1981, 1990; Licata and Rowlett, 2008; Nader et al, 1991; Szostak et al, 1987; Yanagita, 1970; Yanagita and Takahashi, 1973).

Human laboratory studies have shown that these drugs maintain self-administration behaviour (for reviews see Cole and Chiarello, 1990; Griffiths and Weerts, 1997; Griffiths and Wolf, 1990; see also Griffiths and Ator, 1981 and Woods et al, 1987, 1992), although BZDs are generally considered weak reinforcers compared to the self-administration responses elicited by other drugs (opioids, cocaine, amphetamine) (Ator, 2005; Weert et al., 1998; Weerts and Griffiths, 1998). Nevertheless, their easy availability, combined with their positive subjective effects, has made BZDs a widely abused class of drugs.

Abuse of BZDs is typically defined as recreational, non-medical use for the purpose of getting intoxicated or 'high' (Griffiths and Johnson, 2005). However, there remains a provocative debate as to whether BZD abuse is recreational or medical adjunctive (aberrant drug use associated with the therapeutic utility of the drug) in nature (Rosenbaum et al, 2005). In any case, reports of abusive patterns of use began to emerge soon after the widespread clinical use of GABAA agonists and allosteric modulators (Ator and Griffiths, 1987; Bergman and Griffiths, 1986; Strang et al., 1994). There is considerable evidence to suggest that benzodiazepine misuse remains widespread. The 2010 National Survey on Drug Use and Health found that there were an estimated 186,000 new users of benzodiazepines (Substance Abuse and Mental Health Services Administration, 2010). According to the Treatment Episode Data Set (TEDS), the number of people seeking treatment for BZD abuse nearly tripled between 1998 and 2008 (Substance Abuse and Mental Health Services Administration, 2011b). Data also indicate that benzodiazepines are often abused in combination with other drugs, most commonly opioids (Crane and Nemanski, 2004; Substance Abuse and Mental Health Services Administration, 2011b).

6 PHARMACOLOGICAL INTERACTIONS BETWEEN OPIOIDS AND BENZODIAZEPINES

Several studies have attempted to elucidate the mechanisms underlying the co-abuse of opioids and BZDs by examining how these two types of drugs interact.

Preclinical research has shown that opioids and BZDs have significant modulatory effects on each other (Duka et al, 1980; LaBuda and Fuchs, 2001; Lopez et al, 1990; Moroni et al, 1978; Rocha et al, 1993; Sasaki et al, 2002; Soria et al, 1991; Tien, 2007). One possible mechanism to explain this modulatory interaction is that BZDs may alter the pharmacokinetics of opioids. For example, Spaulding et al. (1974) studied hepatic methadone concentrations following different doses of diazepam in methadone-dependent rats. They found that diazepam was a non-competitive inhibitor of methadone metabolism. Shah et al (1979) and Liu et al (1978) also reported that when diazepam was administered one hour before methadone, there was an increase in methadone concentrations in liver and brain tissue and a decrease in urinary and hepatic methadone metabolites. Research using human liver microsomes also showed that N- N-demethylation of methadone by the liver enzyme CYP3A4 was competitively inhibited by diazepam (Iribarne et al. 1997).

Chang and Moody (2005) also used human liver microsomes and examined the effects of several BZDs on the metabolism of buprenorphine (a partial μ-receptor agonist and κ-receptor antagonist, partly metabolised by CYP3A4). They found that a BZD (midazolam) inhibited the rate of metabolism of buprenorphine. However, other studies suggest that there is not always a pharmacokinetic interaction between BZDs and buprenorphine. Megarbane et al

(2005) found that pretreatment with flunitrazepam did not alter the plasma or striatal kinetics of buprenorphine in rats. Kilicarslan and Sellers (2000) examined the effect of the same drugs in human liver microsomes and again found that co-administration did not alter the plasma concentration or kinetics of either drug.

Although studies suggest that BZDs may inhibit the metabolism of some opioid drugs, BZDs are weak competitive inhibitors of CYP3A4, only one of several hepatic enzymes that metabolise these drugs (Moody et al, 2004). Therefore, this inhibition may not always be sufficient to cause clinically relevant interactions. The few clinical studies in this area seem to support this conclusion (Table 1). Pond et al (1982) studied the effects of 9 days of oral diazepam treatment in methadone-treated patients. No differences in plasma levels of methadone or its metabolites were reported. Another clinical trial investigated the effects of two doses of diazepam in combination with different doses of methadone (Preston et al., 1986). Analysis of plasma drug levels did not indicate any pharmacokinetic interaction.

Although some studies suggest that BZDs and opioids alter each other's pharmacokinetic effects, this interaction may have limited clinical significance. Therefore, many believe that it is the pharmacodynamic interactions of these drugs that underlie their co-abuse. There is considerable preclinical evidence to suggest that the analgesic (Pick, 1997), hyperphagic/hyperdipsic (Cooper, 1983), anxiolytic (Agmo et al, 1995; Primeaux et al, 2006) and rewarding (Lorens and Sainati, 1978; Spyraki et al, 1985) effects of BZDs are mediated in part via opioidergic mechanisms. However, some studies have failed to find this interaction (LaBuda and Fuchs, 2001; Soubrie et al., 1980; Tripp and McNaughton, 1987). Contrasting data have also been reported on the role of BZDs and GABA in opioid analgesia (Fennesy and Sawynok, 1973; Ho et al., 1976; Ito et al., 2008; Mantegazza et al., 1979; Palauglu and Ayhan, 1986; Sivman and Ho, 1985; Yoneda et al., 1976; Zonta et al., 1981).

Preclinical evidence that BZDs enhance the rewarding and reinforcing effects of opioids may provide the best indication of why these drugs are co-used (Panlilio et al, 2005; Walker and Ettenberg, 2001, 2003, 2005). In particular, individuals may use opioids and BZDs together to enhance the μ-agonist effects of opioids (e.g. opioid intoxication). For example, Stitzer and colleagues (1981) reported that 72% of methadone patients who were regular benzodiazepine users reported using diazepam to enhance the effects of their daily methadone dose. Similarly, heroin users reported that the intensity and duration of the heroin effect was prolonged by the addition of intravenous flurazepam (Strang, 1984). Chen and colleagues (2011) also found that among methadone clients who reported a history of BZD use, 45.5 % reported that they used to: "get high", "have a good time" or "have an intense, exciting experience".

Few clinical studies have examined the effects of BZDs in combination with opioids under controlled laboratory conditions (Table 1). One such study, conducted by Preston and colleagues (1984) in methadone-maintained patients, found that two doses of oral diazepam (20 and 40 mg) given in combination with various doses of methadone (between 50-120 mg) produced greater pupil constriction (an indicator of μ-agonist effects) than either drug alone (diazepam alone has no effect on pupil diameter: Hou et al., 2006; Sigg et al., 1971). Their study also assessed subjective effects using a visual analogue scale. They found that methadone in combination with the highest dose of diazepam produced greater opioid-like effects than methadone alone.

These findings were later confirmed by several studies reporting similar interactions (Farre et al., 1998; Lintzeris et al., 2006; 2007; see review by Lintzeris and Nielsen, 2010). For example, Lintzeris and colleagues (2007) found that co-administration of diazepam (40 mg) with methadone or buprenorphine was associated with increases in peak subjective ratings of 'strength of drug effect' and 'sedation' compared with each opioid alone. These researchers also reported similar results with lower "therapeutic" doses of diazepam (10, 20 mg; Lintzeris et al., 2006). Positive subjective effects (e.g. 'liking' the drug) are generally correlated with the reinforcing effects of a drug and are therefore an indicator of its abuse potential (Griffiths and Johnson, 2005; Lynch and Carroll, 2001). In support of this idea, Spiga and colleagues (2001) found that pretreatment with diazepam produced dose-related increases in subjective ratings of drug 'liking', 'high', 'strength of drug effect' and 'good effects', as well as dose-related increases in methadone self-administration in methadone-maintained participants.

7 THE CO-ABUSE OF BENZODIAZEPINES AND OPIOIDS IN HUMANS

Research suggests that the abuse liability of BZDs may be notable only in certain clinical populations,

notably recreational users of other drugs of abuse and detoxified alcoholics (Cole and Chiarello, 1990). In addition, abuse of BZDs has been consistently reported in the literature in patients maintained on opioid agonists such as methadone and, more recently, buprenorphine (Barnas et al., 1992, Brands et al., 2008; Kleber and Gold, 1978).

The prevalence of BZD use among methadone-maintained clients (identified by positive urine tests) ranges from 51 % to 70 % (Gelkopf et al., 1999; Hartog and Tusel, 1987; San et al., 1993; Stitzer et al., 1981). Rates in this range have also been reported for buprenorphine maintenance clients (Lavie et al., 2009; Neilsen et al., 2007; Thirion et al., 2002) and active heroin users (Darke et al., 1992, 1995).

The US Treatment Outcome Prospective Study (TOPS) found that 73 % of heroin users entering treatment reported BZD use in the previous year (Du pont, 1988). Almost 25% of these individuals reported daily use of BZDs. Similarly, 65-70% of methadone-maintained patients in Baltimore (n=12) and Philadelphia (n=17) were found to have positive urine screens for BZDs within a single month. This study also reported the 6-month prevalence of more than 50% of urine tests positive for BZDs: Baltimore = 80%, Philadelphia = 47.9% (Stitzer et al., 1981). A later study using a much larger sample (n= 547) found a similar 6-month prevalence of sedative use among methadone clients in three US cities (Baltimore = 66%, Philadelphia = 53% and New York City = 44%; Iguchi et al., 1993; see also Iguchi et al., 1989). This study also reported a high lifetime prevalence of sedative use among clients of methadone clinics: Baltimore = 94%, Philadelphia = 78%, New York City = 86%. Although this study assessed the use of BZDs and barbiturates, rates of barbiturate use were much lower.

Since these studies, there has been little research in the US on BZD use among patients on opioid replacement therapy (but see Chen et al, 2011). However, recent studies in Europe continue to show a high prevalence of opioid and BZD co-use. A survey conducted in France among buprenorphine-maintained patients reported a lifetime prevalence of benzodiazepine use of 67 % and a 30-day prevalence of 54 % (Lavie et al., 2009; see also Laqueille et al., 2009). In Spain, a study of patients in methadone treatment programmes found that 46.5 % were regular users of BZDs (Fernández-Sobrino et al., 2009). These figures were closely matched by a Swiss study, which reported that 51.5% of patients in a methadone maintenance programme were 'regular' BZD users (Meiler et al., 2005). In Germany, weekly urine screening for BZD use was carried out among patients in heroin-assisted treatment and methadone maintenance. This study found that the weekly average of BZD-positive tests was 52.3 % for heroin-assisted treatment and 60.3 % for methadone maintenance (Eiroa-Orosa et al., 2010). A more recent German study found even higher rates of BZD-positive tests among methadone clients (70%; Specka et al., 2011).

Most European studies have reported rates of acute benzodiazepine use among methadone and buprenorphine clients similar to those reported in the USA, with comparatively lower rates of BZD use reported in similar UK populations. In samples of patients in methadone treatment, estimates of daily BZD use have been reported to be around 35%, with over 50% of the sample reporting multiple uses per month (Metzger et al., 1991).

A number of studies have found not only significant BZD misuse among these populations, but also significant levels of physical dependence on BZDs. Other studies have found that between 18% and 54% of those newly admitted to methadone treatment also required detoxification from BZDs (Gelkopf et al., 1999; Rooney et al., 1999; Specka et al., 2011). Researchers concluded that these findings indicate a high prevalence of physical dependence on BZDs among heroin users seeking treatment. A similar prevalence of BZD dependence was found in an Australian study, where 22 % of heroin users had a current diagnosis of benzodiazepine dependence (Darke et al., 1993).

In several of their studies, Darke and colleagues have consistently found recurrent patterns of BZD use among heroin/methadone users (Darke et al., 2010; Darke and Hall, 1995; Darke and Ross, 1997). In 1993, they reported that 26.6% of methadone clients admitted daily benzodiazepine use (Darke et al., 1993). In another study, 41 % of heroin users reported using BZDs weekly (or more) in the last few months (Ross et al., 1996). Subsequent research found that 1 in 3 heroin users had been prescribed a BZD in the previous month (Darke et al., 2003), 2 in 3 heroin users reported non-medical use of BZDs in the previous year and 91 % reported lifetime use (Ross and Darke, 2000).

In addition to demonstrating the prevalence and frequency of BZD use in this population, this type of research has also shown that opioid-dependent populations have a preference for certain BZDs. Preference for diazepam (Du pont, 1988; Iguchi et al., 1993), midazolam (Bruce et al., 2008) and alprazolam (Fernández-Sobrino et al., 2009) has been reported. Another group of researchers used the Norwegian Prescription Database to investigate the prevalence of

BZD use among patients in opioid maintenance treatment. Analysis of this database, which has recorded all prescriptions for the whole population since 2004, showed that 40% had received at least one BZD prescription in the previous year, which is 8 times higher than the general age-matched population in the country. The most commonly sought/prescribed BZD was oxazepam, closely followed by diazepam (Bramness and Kroner, 2007). A report from Malaysia found that almost 75% of a large sample of opioid users (97.6% were heroin users) reported concurrent use of BZDs within the past year (Navaratnamand and Foong, 1990). Diazepam use was relatively uncommon in this sample (1.6%). Flunitrazepam was the most commonly used BZD (51.4%), followed by: alprazolam 10.8%, triazolam 4.4%, lorazepam 4.0%, nimetazepam 2.8% and nitrazepam 0.4%. Similarly, a study in Israel found that of the 66.6% of methadone-maintained patients who regularly misused BZDs, 92.9% regularly used flunitrazepam, 54.3% diazepam, 38.6% oxazepam, 20% brotizolam, 20% lorazepam, 15.7% alprazolam and 4.3% nitrazepam (Gelkopf et al., 1999). This survey also found that the doses of BZDs used exceeded the normal therapeutic range, with the mean maximum amount of BZDs abused per day equivalent to 93.2 mg of diazepam (the maximum daily dose recommended by the FDA is 40 mg of diazepam). However, lower mean daily doses of diazepam (30-45 mg) have been reported in other studies (Dupont, 1988; Iguchi et al., 1993).

8 COMPLICATIONS OF BENZODIAZEPINE AND OPIOID CO-ABUSE

As polydrug use of BZDs and opioids appears to be common, it is important to investigate the potential adverse events that may result. Polydrug use has been shown to be a significant predictor of overdose (Kerr et al, 2005). Data suggest that 62-72% of patients treated for overdose have used more than one drug class (Backmund et al, 1999; Darke et al, 1996). This percentage is even higher (71-98%) when only fatal overdoses are considered (Cook et al., 1998; Grass et al., 2001; New York City Dept. of Health and Mental Hygiene, 2011; Perret et al., 2000; Schmidt-Kittler et al., 2000). Respiratory depression is the primary mechanism of death from opioid overdose (White and Irvine, 1999).

Respiration is mainly controlled by medullary respiratory centres together with input from chemoreceptors and other sources. Opioids inhibit these respiratory centres via μ- and δ-opioid receptors (White and Irvine, 1999). Inhibitory GABA receptors are also highly concentrated in these areas (Skatrud et al, 1988). Therefore, both opioids and BZDs, used separately or concurrently, are capable of altering respiratory rate.

Laboratory studies have investigated the combined effects of these two drugs on breathing. Preclinical research by Gueye and colleagues (2002) found that the combination of high doses of midazolam (160 mg/kg, intraperitoneal) and buprenorphine (30 mg/kg, intravenous) produced rapid and prolonged respiratory depression, greater than either drug alone. Rodents receiving the combination showed significant increases in PaCO2 (partial pressure of arterial carbon dioxide), decreases in arterial pH and PaO2 (partial pressure of arterial oxygen), and delayed hypoxia (deprivation of adequate oxygen supply). Similarly, another study in rodents found that rapid and sustained respiratory depression was only observed when buprenorphine (30 mg/kg, i.v.) and flunitrazepam (40 mg/kg, i.v.) were co-administered (i.e. this dose of buprenorphine alone had no significant effect; Megarbane et al., 2005).

Nielsen and Taylor (2005) performed a similar experiment in rats using multiple doses of two opioids. They found that intraperitoneal (i.p.) pretreatment with diazepam (20 mg/kg) abolished the protective plateau or ceiling effect often observed with increasing doses of buprenorphine (0.03, 0.1, 0.3 mg/kg, i.v.) on respiration (see Walsh et al., 1994 for more on the ceiling effects of buprenorphine). In the same study, pretreatment with diazepam potentiated the dose-dependent inhibition of respiration observed with increasing doses of methadone (0.1, 0.3, 1.0 mg/kg, i.v.; see also similar findings by McCormick et al., 1984 and Borron et al., 2002). As benzodiazepines can have respiratory depressant effects, depending on the dose and route of administration, it remains to be determined whether BZDs act to potentiate this effect of opioids or simply act in an additive manner to depress ventilation (Carraro et al., 2009; Mak et al., 1993; Zacharias et al., 1996). Further studies are warranted to explain the pharmacological interaction that may occur with BZDs and buprenorphine, as well as other opioids.

In one of the few clinical studies to investigate this interaction, patients undergoing anaesthesia were given lorazepam with either fentanyl or buprenorphine. Of the 88 patients enrolled, 11 developed respiratory depression requiring manual

ventilation. All of these 11 participants had received buprenorphine (Faroqui et al, 1983). More recent clinical research has only used lower doses within the therapeutic range (diazepam 0, 10, 20 mg) and has therefore not been able to confirm these findings (Lintzeris et al. 2006). Nevertheless, prolonged respiratory depression after medical use of opioids in combination with BZDs has been observed by anaesthesiologists since the 1980s (Forest, 1983; Papworth, 1983; Sekar and Mimpriss, 1987).

Other clinical data provide more direct evidence of the risks of this drug combination. Clinical studies have shown that the concomitant use of BZDs and opioids is associated with the occurrence of fatal and non-fatal opioid overdoses (Darke et al, 1996; Perret et al, 2000; Schmidt-Kittler et al, 2001). Almost half of all heroin users report at least one non-fatal overdose (Pollini et al., 2006), and BZDs have been identified in 50-80 % of heroin-related deaths (Grass et al., 2003; Oliver and Keen, 2003; Stenhouse and Grieve, 2003; Ward and Barry, 2001).

Opioid agonist treatments also carry a risk of overdose, particularly full agonists such as methadone. A recent retrospective analysis of drug interactions and adverse events in methadone patients found significant evidence of additive CNS and respiratory depression when methadone was combined with benzodiazepines (Lee et al., 2012). Accordingly, BZDs have been implicated in 40-80% of methadone-related deaths (Brugal et al., 2005; Chan et al., 2006; Ernst et al., 2002; Mikolaenko et al., 2002; Pirnay et al., 2004; Wolf et al., 2004; Zador and Sunjic, 2000) and up to 80% of buprenorphine-related deaths (Kintz, 2001; Pirnay et al., 2004; Reynaud et al., 1998).

Although the risk of overdose is low with buprenorphine, this risk increases when buprenorphine is injected and used in combination with other tranquillisers (Corkey et al, 2004; Paulozzi et al, 2009; Pirnay et al, 2004; Vormfeld and Poser, 2001; Walsh et al, 1994; Wolff, 2002). Up to 60% of some samples of heroin users report a history of injecting buprenorphine and BZDs (Vicknasingam et al., 2010). Buprenorphine maintenance is becoming a common treatment for opioid dependence, and human laboratory studies of combined opioid and BZD use are limited. A study by Reynaud et al (1998) examined the post-mortem analysis of opioid-dependent individuals. Urine, blood and tissue samples were analysed and no medications other than buprenorphine and a BZD drug were found to have contributed to the deaths.

Another complication of the combined use of opioids and BZDs is the antidotal treatment of acute overdose or intoxication. Naloxone is well known for the treatment of opioid overdose. In an effort to reduce the number of deaths from opioid overdose, programmes have been implemented in parts of Australia, the United States and the United Kingdom to prescribe naloxone to non-medical practitioners for administration in suspected cases of opioid overdose. The concomitant use of BZDs by the opioid users targeted by these programmes may make it more difficult for typically prescribed doses of naloxone to reverse respiratory depression.

We know that naloxone is effective in the treatment of opioid overdose, but we do not know how concomitant use of BZDs might alter this. However, there are preclinical data suggesting that naloxone may also be of direct benefit in the treatment of BZD overdose (Dingledine et al, 1978; Soubree' et al, 1980). A retrospective analysis found that the addition of between 0.2 and 1.0 mg of flumazenil (a GABAA receptor antagonist) to low doses of naloxone (0.4-0.8 mg) improved mental function in patients following buprenorphine overdose in whom BZDs were co-ingested (Me'garbane et al., 2010). Although caution should be exercised in the use of flumazenil due to the risk of seizures and the need for close monitoring during administration, these data suggest that flumazenil and naloxone may serve as an antidotal treatment in cases of benzodiazepine and opioid overdose.

There are no prospective human studies evaluating how the co-administration of BZDs may alter the effectiveness of naloxone in reversing opioid overdose. More clinical data are also needed to evaluate novel treatment approaches using naloxone for BZD overdose. In any case, naloxone is an interesting and important consideration in the treatment of opioid and BZD co-abuse.

In addition to the potential to exacerbate drug-related harm, the co-abuse of opioids and BZDs is further complicated by the possibility of physical dependence on and withdrawal from opioids and BZDs (Puntillo et al, 1997). Clinical indicators of opioid withdrawal include: abdominal cramps, diarrhoea, bone and muscle pain, insomnia and anxiety (Herridge and Gold, 1988). Symptoms of benzodiazepine withdrawal include autonomic instability, increased anxiety, fear, dread, restlessness, confusion and panic attacks. Abrupt BZD withdrawal can lead to fatal refractory seizures (Durbin, 1994). Traditional therapeutic approaches to BZD dependence that have been used in opioid users include tapered detoxification with barbiturates, long-acting BZDs and/or antiepileptics (Bleich et al, 2002; Kristensen et al, 2006; McDuff et al, 1993; McGregor

et al, 2003; Ravi et al, 1990).

Some researchers have also suggested BZD maintenance strategies for people on agonist maintenance treatment (Weizman et al, 2003). Although this may prove to be a useful treatment modality, clinicians and treatment providers may be reluctant to maintain BZD dependence because of the risks described above and the lack of evidence-based justification. In any case, studies focusing on polydrug detoxification are scarce and the effectiveness of these strategies has not been extensively investigated.

Further complicating the treatment prognosis for this population, studies have found that, compared with individuals who abuse only opioids, BZD and opioid polydrug abusers: have a significantly longer duration of opioid use, use higher doses of opioids, and are more likely to abuse additional drugs (excluding BZDs) (Meiler et al., 2005; Rooney et al., 1999; Ross et al., 1996, 2000). Meiler et al (2005) reported that among methadone-maintained patients, those who were regular BZD users received higher daily methadone doses and were more likely to abuse alcohol. Similarly, a study by Ross and Darke (2000) found that heroin users with a lifetime diagnosis of dependence on BZDs were more likely to have a lifetime diagnosis of alcohol dependence (83 % vs. 60 %) and cocaine dependence (23 % vs. 4 %) than those with no lifetime diagnosis of dependence on BZDs. Given these findings, it is not surprising that research has shown poorer treatment outcomes for these polydrug users. Although it has not been shown to alter retention in methadone maintenance, BZD use during methadone maintenance is associated with poorer treatment outcomes in terms of general health, legal problems and alcohol use (Brands et al., 2008; Eiroa-Orosa et al., 2010).

The increased negative factors associated with BZD and opioid polydrug use also extend to psychological variables. Compared with a control group of heroin users, heroin users who were physically dependent on BZDs were much more likely to use antidepressants daily and more likely to report a history of depression, including thoughts of self-harm (Rooney et al, 1999). Other studies have also found an increased frequency of psychiatric comorbidity in this population. Studies have shown that opioid users who regularly use BZDs are almost three times more likely to have had a psychiatric hospital admission in the previous year. They are also almost twice as likely to have been prescribed medication for emotional problems and have a much poorer psychiatric status (Eiroa-Orosa et al., 2010). Other research has found higher rates of anxiety and depressive disorders in similar comparisons (Rooney et al., 1999; Ross and Darke, 2000).

Opioid users who abuse BZDs have also been shown to report behaviours associated with increased risk of HIV and hepatitis C (HCV) infection, such as injecting more frequently and sharing injecting equipment more frequently and with more people (Breen et al, 2004; Darke et al, 1992, 1995; Forsyth et al, 1993; Kintz et al, 2001; Klee et al, 1990). However, studies directly comparing the prevalence of blood-borne diseases between opioid users who co-abuse BZDs and those who do not are few and have reported conflicting results. Meiler et al. (2005) found no significant differences in HCV and HIV infection between methadone clients who regularly use BZDs and those who do not. In contrast, Bleich et al, (1999) found significantly increased rates of HCV in a cohort of methadone clients who also abused BZDs. Although research has shown that polysubstance abuse typically increases rates of HCV and HIV infection, more data are needed to specifically assess the impact of combined BZD use on rates of infectious disease transmission among opioid users (Backmund et al., 2005, Nurutdinova et al., 2011).

9 CONCLUSIONS

There is ample evidence of significant co-use of BZDs and opioids. Opioids have considerable therapeutic utility, but their euphoric effects make them among the most commonly abused drugs in the world. Compared with opioids, BZDs are thought to have very limited euphoric effects and, when used alone, are less likely to be abused. Drug users appear to have discovered that BZDs can enhance the positive subjective effects of opioids. Thus, individuals may combine opioids and BZDs to achieve greater levels of euphoria. Further clinical studies are needed to investigate these hypotheses in controlled laboratory settings.

People in opioid substitution treatment worldwide appear to be particularly vulnerable to co-abuse of opioids and BZDs. It appears that the addition of the BZD drug to methadone or buprenorphine may allow them to achieve a more potent opioid effect, often described as 'heroin-like'. Further research is needed to clarify the increased abuse potential of this drug combination. Do BZDs enhance the reinforcing effects of opioids? Or is the increased abuse potential simply an additive effect of combining two reinforcing drugs? Individuals with chronic pain who use prescription opioids may use BZDs to enhance the euphoric effects of their opioids. Anecdotal

reports from users and clinical data showing that these individuals do not use therapeutic doses suggest that BZD use among these individuals is primarily recreational. However, the possibility remains that prescription opioid users may be self-medicating for inadequate pain management or co-occurring mood or anxiety disorders. These types of conditions, for which BZDs are effective, are common among heroin users. Studies examining the prevalence of affective and anxiety disorders among co-users of prescription opioids and BZDs may help to determine whether their co-use is recreational or therapeutic.

Future studies should also look at how these people obtain BZDs. There is a wealth of research showing the many ways in which people obtain prescription opioids. Opioid abusers often: forge prescriptions, obtain opioids from friends and family, attend emergency departments with complaints of pain, or buy opioids on the street (Ballantyne and LaForge, 2007; Fishbain et al., 1992). This knowledge of the liability of opioid misuse has raised awareness among health care professionals, and greater caution is required when considering patients for opioid therapy. Research has shown that BZDs are the most commonly sold controlled prescription drug on the Internet, with 89% of these sites selling these drugs without a prescription (National Center on Addiction and Substance Abuse at Columbia University, 2006). This study also found that 70% of the sites requiring a prescription allowed the prescription to be faxed, creating the potential for individuals to forge or alter prescriptions or send the same prescription to multiple sites. There is also a trend towards online consultation rather than a prescription. In this case, the consumer fills in an online questionnaire, which is reportedly evaluated by a doctor associated with the online pharmacy. Less is known about the prevalence of illegal street sales of BZDs. A high incidence of questionable internet 'prescriptions' and street sales may suggest the need for stricter national policies to regulate the availability of these drugs. On the other hand, if BZDs are mainly obtained through doctors, this may suggest the need for increased vigilance on the part of doctors. Much is still unknown about the interactions between opioids and BZDs. Although BZDs are widely used in the treatment of anxiety disorders, efforts must be made to prevent the potentially lethal interaction that can occur when opioids and BZDs are administered concomitantly. Benzodiazepines have been shown to abolish the protective ceiling effect of buprenorphine on respiratory depression, an important benefit of this treatment. In opioid-using populations, clinicians may wish to consider non-CNS depressants such as low-toxicity antidepressants (i.e. SSRIs), atypical antipsychotics or buspirone instead of BZDs. Non-pharmacological treatments such as imagery, distraction, meditation and desensitisation could also be considered as initial or adjunctive treatment for anxiety disorders.

This review also raises important questions about how to treat people who co-abuse these two drugs. This issue is complicated by the possibility of dual physical dependence on opioids and BZDs in these individuals. More research is needed into the safety and benefits of BZD maintenance strategies, although they may not prove to be a viable treatment approach. Future studies investigating the administration of the opioid antagonist naloxone may prove useful in the treatment of combined BZD and opioid overdose. When used together, the combination of opioids and BZDs has serious adverse effects on physical and mental health and sobriety. In addition to increasing the risk of overdose, polydrug use of BZDs and opioids can exacerbate the criminal, psychological and medical problems commonly seen in drug users. Therefore, we recommend that prescribers be vigilant for patterns of misuse in patients receiving one or both types of medication. Drug treatment centres should also warn users of the risks of this drug combination and encourage treatment for abuse of both drugs.

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