



Published in final edited form as:

Drug Alcohol Depend. 2012 September 1; 125(1-2): 8–18. doi:10.1016/j.drugalcdep.2012.07.004.

Polydrug abuse: A review of opioid and benzodiazepine combination use

Jermaine D. Jones¹, Shanthi Mogali¹, and Sandra D. Comer¹

¹Division on Substance Abuse, New York Psychiatric Institute and Department of Psychiatry, College of Physicians and Surgeons of Columbia University, 1051 Riverside Drive, Unit 120, New York, NY 10032, USA

Abstract

This paper reviews studies examining the pharmacological interactions and epidemiology of the combined use of opioids and benzodiazepines (BZD). A search of English language publications from 1970 - 2012 was conducted using PubMed and PsycINFO®. Our search found approximately 200 articles appropriate for inclusion in this paper. While numerous reports indicate that the co-abuse of opioids and BZDs is ubiquitous around the world, the reasons for the co-abuse of these medications are not entirely clear. Though the possibility remains that opioid (ab)users are using BZDs therapeutically to self-medicate anxiety, mania or insomnia, the data reviewed in this paper suggest that BZD use is primarily recreational. For example, co-users report seeking BZD prescriptions for the purpose of enhancing opioid intoxication or “high,” and use doses that exceed the therapeutic range. Since there are few clinical studies investigating the pharmacological interaction and abuse liability of their combined use, this hypothesis has not been extensively evaluated in clinical settings. As such, our analysis encourages further systematic investigation of BZD abuse among opioid users. The co-abuse of BZDs and opioids is substantial and has negative consequences for general health, overdose lethality, and treatment outcome. Physicians should address this important and underappreciated problem with more cautious prescribing practices, and increased vigilance for abusive patterns of use.

Keywords

Opioids; heroin; benzodiazepines; polydrug abuse

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Correspondence concerning this article should be addressed to: Sandra D. Comer, New York State Psychiatric Institute, College of Physicians and Surgeons of Columbia University, 1051 Riverside Drive, Unit 120, New York, NY 10032, USA, Phone (212) 543-5981, FAX (212) 543-5991, sdc10@columbia.edu.

Contributors

Dr. Jones constructed sections describing the basic pharmacology of opioids and benzodiazepines, their physiological interactions and prevalence of their co-use around the world. Dr. Mogali described the abuse of these two drugs in human populations, along with its clinical implications and dangers. Dr. Comer wrote sections describing the significance and impact of this research and synthesized the various sections into one cohesive manuscript. All authors have approved the final manuscript.

Conflicts of Interest

Only the authors listed are responsible for the content and preparation of this manuscript. The authors declare that over the past three years SDC, JDJ, and SM have all received compensation (in the form of partial salary support) from investigator-initiated studies supported by Reckitt-Benckiser Pharmaceuticals, Schering-Plough Corporation, Johnson & Johnson Pharmaceutical Research & Development, Endo Pharmaceuticals, and MediciNova. In addition, SDC has served as a consultant to the following companies: Abbott, Alpharma, Analgesic Research, BioDelivery Sciences, Cephalon, Inflexxion, King, Neuromed, Purdue, and Shire.

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1. INTRODUCTION

Benzodiazepines and opioids are among the most frequently abused psychoactive drug classes in the world (Grytten, 1998; Joranson et al., 2000; Substance Abuse and Mental Health Services Administration, 2008). Not surprisingly, the concomitant use of these two classes of drug has received the attention of researchers and physicians since the 1970's (Kleber and Gold, 1978). The goal of this review is to gain a better understanding of the motivations for, and consequences of their co-use. Using PubMed and PsycINFO we searched for English language articles on this topic published between 1970 and 2012. Various 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. With this method, we identified over 5,000 publications. After the removal of duplicates, titles and/or abstracts were reviewed by the authors for relevance. Data from approximately 200 articles was included in this manuscript. This review and synthesis of that literature focuses on clinical studies investigating 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 supplement these findings and support the authors' supposition concerning the motivation and risks that underlie the combined use of opioids and BZDs.

This review begins with a brief overview of the abuse of each drug alone, followed by a review of clinical literature investigating how opioid and BZD drugs interact pharmacologically. Finally, we review reports relating to the prevalence and consequences of BZD and opioid co-abuse. It is our hope that this review will lead to a better understanding of: how these drugs interact pharmacologically, which populations are abusing these two drugs and why, the prevalence of their co-abuse, and the clinical implications of this behavior.

2. 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 actions: they alter body temperature, cause sedation, depress respiration, induce eating, decrease gastrointestinal transit, affect urinary output, and produce either euphoria or dysphoria (Broekkamp et al., 1984; Teasdale et al., 1981; Wise, 1989). These effects are primarily produced through actions at the three opioid receptor subtypes: μ , κ , and δ . Of the subtypes, the μ -opioid receptor is the most well known and studied. Activation of the G protein-coupled μ receptor leads to acute changes in neuronal excitability. It is the agonist actions of opioids upon μ receptors that are thought to underlie their ability to relieve pain, suppress coughing, and alleviate diarrhea. Unfortunately, μ receptors also appear to mediate the abuse potential of many opioid drugs (Bertalmio and Woods, 1989; Matthes et al., 1996; Negus et al., 1993; Spragg et al., 1940).

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 condition place preference (CPP) paradigms are commonly used to examine 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 (see Kieffer and Gavériaux-Ruff, 2002; Preston and Jasinki, 1991 and Trigo et al., 2010 for reviews). This research demonstrates that heroin has considerable abuse potential, and epidemiologically its abuse is a significant public health concern (Comer et al., 2008b; European Monitoring Center for Drug and Alcohol Dependence, 2010; Jasinski and Preston, 1986).

It is estimated that 9.2 million people worldwide are regular heroin users, with an estimated 1.2 million active heroin users in the U.S. (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, approximately 180,000 persons over the age of 12 used heroin for the first time. In this same year, 507,000 individuals sought treatment for heroin use and nearly 20% (> 200,000) of all emergency department visits involving 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 opioid drugs, including morphine, hydrocodone, hydromorphone, fentanyl, buprenorphine and oxycodone, have also demonstrated significant abuse liability in humans (Comer et al., 2008b; Middleton et al., 2011; Walsh et al., 2008; Zacny and Lichtor, 2008). The abuse of buprenorphine has been particularly prevalent in Europe where widespread buprenorphine treatment was in place several years prior to its use in the U.S (Auriacombe et al., 2001; Carrieri et al., 2006). The United States has observed a steep rise in the recreational use of prescription opioid analgesics during the past two decades. Data from epidemiological investigations, treatment admissions, and emergency room records also indicate an increasing prevalence of prescription opioid abuse (Cicero, 2005; Gilson et al., 2004; Substance Abuse and Mental Health Services Administration, 2010). In some parts of the U.S., unintentional drug poisoning deaths caused by 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) revealed that the number of new initiates to non-medical use of opioid analgesics (2.2 million) was only exceeded by that of marijuana (2.4 million), surpassing well-known drugs of abuse like cocaine (0.6 million), methamphetamine (0.15 million), and ecstasy (1.1 million; Substance Abuse and Mental Health Services Administration, 2010). Recent estimates place the prevalence of past-year non-medical use of prescription opioids at approximately 5.3 million, with as many as 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 commonly abused in combination with benzodiazepine-type drugs. Together opioids and BZDs constituted the majority of ED visits involving non-medical use of psychotherapeutics (Substance Abuse and Mental Health Services Administration, 2011a).

3. A BRIEF OVERVIEW ON BENZODIAZEPINE ABUSE

Benzodiazepines are among the most frequently prescribed psychotropic drugs in the world (Coach, 1990). These drugs, whose core chemical structure is the fusion of a benzene and diazepine ring, act as positive allosteric modulators of the GABA_A receptor complex. Benzodiazepines act to enhance the effects of GABA by increasing chloride (Cl⁻) flux and rate of channel opening. These drugs are a commonly used and effective treatment for anxiety disorders, and adjunctive treatment in several psychiatric and neurological illnesses (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_A

subunits has been implicated in their sedative and anxiolytic actions (Low et al., 2000; McKernan et al., 2000). Unlike some of their other effects, the reinforcing effects of BZD are not easily attributed to a single receptor subtype (Licata and Rowlett, 2008). A number of BZDs have been shown to serve 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 demonstrated that these drugs do maintain self-administration behavior (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), though in comparison to the self-administration responses elicited by other drugs (opioids, cocaine, amphetamine), BZDs are generally thought of as weak reinforcers (Ator, 2005; Weert et al., 1998; Weerts and Griffiths, 1998). Nevertheless, their easy availability combined with their positive subjective effects has made BZDs a commonly abused class of drug.

Abuse of BZDs is typically defined as recreational, non-medical use for the purpose of becoming intoxicated or “high” (Griffiths and Johnson, 2005). Yet, there continues to be provocative debate concerning whether BZD abuse is recreational or medically adjunctive (aberrant drug use associated with the therapeutic utility of the drug) in nature (Rosenbaum et al., 2005). In either case, soon after the widespread clinical use of $GABA_A$ agonists and allosteric modulators, reports of abusive patterns of use began to emerge (Ator and Griffiths, 1987; Bergman and Griffiths, 1986; Strang et al., 1994). An abundance of evidence suggests that benzodiazepine abuse remains prevalent. The 2010 National Survey on Drug Use and Health found that there were an estimated 186,000 new abusers of benzodiazepine drugs (Substance Abuse and Mental Health Services Administration, 2010). According to the Treatment Episode Data Set (TEDS), the number of individuals seeking treatment for BZD abuse nearly tripled between 1998 and 2008 (Substance Abuse and Mental Health Services Administration, 2011b). The data also indicate that benzodiazepines are commonly abused in conjunction with other drugs, most frequently opioids (Crane and Nemanski, 2004; Substance Abuse and Mental Health Services Administration, 2011b).

4. PHARMACOLOGICAL INTERACTIONS BETWEEN OPIOIDS AND BENZODIAZEPINES

A number of studies have attempted to elucidate the mechanisms underlying opioid and BZD co-abuse by examining how these two types of drugs interact with one another. Preclinical research has shown that opioids and BZDs exert significant modulatory effects upon one another (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. Spaulding et al. (1974), for example, examined liver methadone concentrations following various diazepam doses in methadone-dependent rats. His investigation revealed that diazepam was a noncompetitive inhibitor of methadone metabolism. Shah et al. (1979) and Liu et al. (1978) also reported that when diazepam was administered 1-hour prior to methadone, an increase in methadone concentrations occurred in hepatic and brain tissues along with decreased urinary and hepatic methadone metabolites. Research using human liver microsomes also demonstrated that N-demethylation of methadone by liver enzyme CYP3A4 was competitively inhibited by diazepam (Iribarne et al. 1997).

Chang and Moody (2005) also utilized human liver microsomes and examined the effects of multiple BZDs upon the metabolism of buprenorphine (a partial μ receptor agonist and κ receptor antagonist, metabolized in part by CYP3A4). Their investigation found that one BZD (midazolam) inhibited the rate of buprenorphine metabolism. However, other studies suggest that a pharmacokinetic interaction does not always exist between BZDs and buprenorphine. Megarbane et al. (2005) found that in rats, flunitrazepam pretreatment failed to alter the plasma or striatal kinetics of buprenorphine. Kilicarslan and Sellers (2000) examined the effect of the same drugs in human liver microsomes, again finding that co-administration did not alter the plasma concentration or kinetics of either.

Though studies suggest that BZDs are capable of inhibiting the metabolism of some opioid drugs, BZDs are weak competitive inhibitors of CYP3A4, only one of the several hepatic enzymes that metabolize these drugs (Moody et al., 2004). Thus, this inhibition may not always be sufficient to produce clinically relevant interactions. The few clinical studies in this area seem to support this conclusion (Table 1). Pond et al. (1982) examined the effects of 9 days of treatment with oral diazepam in methadone-treated patients. No differences were reported in plasma levels of methadone or its metabolites. Another clinical investigation examined the effects of two doses of diazepam in combination with various methadone doses (Preston et al., 1986). Plasma drug level analysis did not indicate a pharmacokinetic interaction.

Although a few studies do suggest that BZDs and opioids alter the pharmacokinetic effects of one another, this interaction may have limited clinical significance. As such, 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; Spyraiki et al., 1985) effects of BZDs are partially mediated via opioidergic mechanisms. Yet, some studies have failed to find this interaction (LaBuda and Fuchs, 2001; Soubrie et al., 1980; Tripp and McNaughton, 1987). Contrasting data has also been reported concerning 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 increase the rewarding and reinforcing effects of opioids may give us the best indication of why these drugs are used concomitantly (Panlilio et al., 2005; Walker and Ettenberg, 2001, 2003, 2005). Specifically, individuals may be co-using opioids and BZDs in order to amplify the μ agonist effects of opioids (e.g. opioid intoxication). Stitzer and colleagues (1981), for example, reported that 72% of methadone-maintained patients who were regular benzodiazepine users indicated that diazepam was used to enhance the effects of their daily methadone dose. Similarly, heroin users reported that the intensity and duration of the heroin effect was extended with the addition of intravenous flurazepam (Strang, 1984). Chen and colleagues (2011) also found that among methadone patients reporting a history of BZD use, 45.5% responded that they used to: “get high,” “have a good time,” or “produce an intense, exciting experience.”

Few clinical studies have investigated 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 pupillary 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 investigation 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 when compared to methadone alone.

These results were later corroborated by several studies reporting similar interactions (Farre et al., 1998; Lintzeris et al., 2006; 2007; see the 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” when compared to each opioid alone. These researchers also reported similar results using lower “therapeutic” doses of diazepam (10, 20 mg; Lintzeris et al., 2006). Positive subjective effects (e.g., drug “liking”) generally are correlated with a drug’s reinforcing effects, and consequently are an indicator of their abuse liability (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 by methadone-maintained participants.

5. THE CO-ABUSE OF BENZODIAZEPINES AND OPIOIDS IN HUMANS

Research suggests that the abuse liability of BZDs may only be notable in certain clinical populations, specifically, recreational users of other drugs of abuse and detoxified alcoholics (Cole and Chiarello, 1990). Furthermore, the abuse of BZDs among patients maintained on opioid agonists such as methadone, and more recently, buprenorphine has been consistently reported in the literature (Barnas et al., 1992, Brands et al., 2008; Kleber and Gold, 1978). The prevalence of BZD use among methadone-maintained patients (identified by positive urinalysis) ranges between 51% and 70% (Gelkopf et al., 1999; Hartog and Tusel, 1987; San et al., 1993; Stitzer et al., 1981). Rates roughly within this range also have been reported for buprenorphine-maintained patients (Lavie et al., 2009; Neilsen et al., 2007; Thirion et al., 2002) and active heroin users (Darke et al., 1992, 1995).

The U.S. Treatment Outcome Prospective Study (TOPS) found that 73% of heroin users entering into treatment reported BZD use in the preceding year (Du pont, 1988). Nearly 25% of these individuals reported daily BZD use. Similarly, it has been found that 65-70% of methadone-maintained patients in Baltimore (n= 12) and Philadelphia (n=17) had positive urinalysis tests for BZDs within a single month. In this study, the 6-month prevalence of having greater than 50% of urine tests positive for BZDs also was reported: Baltimore = 80%, Philadelphia = 47.9% (Stitzer et al., 1981). A later study utilizing a much larger sample (n= 547), found a similar 6-month prevalence of sedative use among methadone patients in three U.S. cities (Baltimore = 66%, Philadelphia = 53%, and New York City = 44%; Iguchi et al., 1993 see also Iguchi et al., 1989). This investigation also reported a high lifetime prevalence of sedative use among methadone clinic patients: Baltimore = 94%, Philadelphia = 78%, New York City = 86%. Though this study assessed for the use of BZDs and barbiturates, rates of barbiturate use were much lower.

Since these investigations, little research has been performed in the U.S. concerning BZD use among patients on opioid replacement therapy (though see Chen et al., 2011). However, recent studies conducted in Europe continue to observe a high prevalence of opioid and BZD co-use. An investigation 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 conducted among patients in methadone treatment programs found that 46.5% of the patients regularly take BZDs (Fernández-Sobrino et al., 2009). These figures were closely matched in a Swiss study reporting that 51.5% of patients in a methadone maintenance

program were “regular” BZD users (Meiler et al., 2005). Weekly urine screening for BZD use among patients in heroin-assisted therapy and methadone-maintenance was performed in Germany. This study found that the weekly average for BZD positive tests was 52.3% for heroin-assisted patients and 60.3% for methadone patients (Eiroa-Orosa et al., 2010). A more recent German study found even higher rates of BZD positive tests among methadone patients (70%; Specka et al., 2011).

Most European studies have found rates of acute benzodiazepine use among methadone and buprenorphine patients that are similar to those reported in the U.S. Comparatively less BZD use among similar British populations has been reported. Among samples of methadone treatment patients, estimates of daily BZD use have been reported around 35%, with over 50% of the sample reporting multiple uses per month (Metzger et al., 1991).

A number of investigations have not only identified significant BZD abuse among these populations, but also significant levels of BZD physical dependence. Other studies have revealed that between 18% and 54% of new admits onto methadone therapy also required detoxification from BZDs (Gelkopf et al., 1999; Rooney et al., 1999; Specka et al., 2011). Researchers concluded that these findings point to a high prevalence of BZD physical dependence among treatment-seeking heroin users. A similar prevalence of BZD dependence was also found in an Australian study where 22% of heroin users received a current diagnosis of benzodiazepine dependence (Darke et al., 1993).

In several of their investigations, 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 patients admitted to daily benzodiazepine use (Darke et al., 1993). In another study, 41% of heroin users reported having used BZDs weekly (or more) within recent months (Ross et al., 1996). In subsequent investigations, they found that 1 in 3 heroin users had obtained a prescription for a BZD drug in the preceding month (Darke et al., 2003), 2 out of 3 heroin users reported non-medical BZD use within the past year, and 91% reported a lifetime prevalence (Ross and Darke, 2000).

In addition to demonstrating how widespread and frequent BZD use is among this population, these types of investigations have also shown that opioid-dependent populations show a preference for particular BZD drugs. Samples have reported a preference for diazepam (Du pont, 1988; Iguchi et al., 1993), midazolam (Bruce et al., 2008) and alprazolam (Fernández-Sobrino et al., 2009). Another groups of investigators utilized the Norwegian Prescription Database in order to investigate the prevalence of BZD use among patients in opioid maintenance treatment. Analysis using this database, which has registered all prescriptions for the entire population since 2004, found that 40% received at least one BZD prescription within the past year, 8- times higher than that of the general age-matched population in this country. The most frequently sought/prescribed BZD was oxazepam, closely followed by diazepam (Bramness and Kroner, 2007).

A report from Malaysia found that nearly 75% of a large sample of opioid abusers (97.6% were heroin users) reported simultaneous use of BZDs within the last year (Navaratnam and Foong, 1990). Among this sample, diazepam use was relative uncommon (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%. Likewise, a study in Israel found that among the 66.6% of methadone-maintained patients who regularly abused 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 investigation also revealed that the doses of BZDs used exceeded the normal

therapeutic range, the mean maximum amount of BZDs abused daily equated to 93.2 mg of diazepam (the FDA recommended maximum daily dose is 40 mg of diazepam). However, lower median daily doses of diazepam (30-45 mg) have been observed in other studies (Dupont, 1988; Iguchi et al., 1993).

Like heroin users in and out of treatment, patients with chronic pain are often under long-term opioid therapy (American Academy of Pain Medicine, 1997; Ballantyne and Mao, 2003; Trescot et al., 2006). It has been noted that as many as 40% of these individuals develop aberrant patterns of opioid use such as: obtaining opioids from multiple prescribers, forging prescriptions, stealing opioids, and intranasal or intravenous use of oral opioids (Passik et al., 2006, for a review see Ballantyne and LaForge, 2007 or Fishbain et al., 1992). Research has also discovered a high prevalence of BZD use among patients with chronic pain. Boeuf and Lapeyre-Mestre (2007) analyzed 1,710 abnormal prescription forms, and reported that the most frequently forged prescriptions were for BZDs, benzodiazepine analogues, and opioids (buprenorphine, morphine).

Concerning the possible nonmedical use of BZDs among patients with chronic pain, survey data has revealed that as many as 40–60% of pain patients regularly use BZDs (Hardo and Kennedy, 1991, see also Kouyanou et al., 1997). In an analysis of prescription records, Bachs et al. (2008) found that those codeine users dispensed the highest amounts of the opioid, were significantly more likely to be co-using large amounts of BZDs. Using a more determinate method, Heltsey et al. (2011) found that 15.7% of oral fluid specimens from 6,441 U.S. pain clinic patients were positive for benzodiazepine drugs. While this percentage is much lower than that found in self-report studies, if benzodiazepine use is sporadic (weekly or less), testing a single sample may have only captured a small percentage of those who are co-using.

Although research has yet to investigate whether BZD use by chronic pain patients is primarily recreational or therapeutic, it is known that benzodiazepines provide little therapeutic benefit to most chronic pain causing conditions (King and Strain, 1990). Also, a prospective follow-up (over 4 – 7 years) of patients who initially reported no history of opioid use, found that BZD use was a stronger predictor of future prescription opioid use than musculoskeletal pain/chronic pain (Skurtveit et al., 2010). In addition to these findings, the fact that rates of BZD use among patients with chronic pain are higher than in the general population highlights the need for education among this population concerning the possible risk of combining these two medications, along with vigilance among prescribers for abusive patterns of use (Woods et al., 1992).

6. COMPLICATIONS OF BENZODIAZEPINE AND OPIOID CO-ABUSE

Because BZD and opioid polydrug use appears to be common, it is important to investigate potential adverse events that may result. Polysubstance abuse has been found to be a significant predictor of drug overdose (Kerr et al., 2005). Data indicate that 62-72% of patients being treated for overdose had consumed more than one class of drug (Backmund et al., 1999; Darke et al., 1996). This percentage is even higher (71-98%) when only fatal overdoses are assessed (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 opioid overdose fatality (White and Irvine, 1999). Respiration is controlled principally through medullary respiratory centers along with input from chemoreceptors and other sources. Opioids inhibit these respiratory centers via the μ - and δ -opioid receptors (White and Irvine, 1999). Inhibitory GABA receptors also highly concentrated in these areas (Skatrud et al., 1988). Hence, both opioids and BZDs, used separately or concurrently, are capable of altering respiration frequency.

Laboratory studies have examined the combined effects of these two drugs on respiration. 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 each drug alone. Rodents given the combination demonstrated significant increases in PaCO₂ (partial pressure of arterial carbon dioxide), a decrease in arterial pH, and PaO₂ (partial pressure of arterial oxygen), along with delayed hypoxia (deprivation of adequate oxygen supply). Similarly, another study conducted 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 administered together (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, employing multiple doses of two opioids. They found that intraperitoneal (i.p.) diazepam pretreatment (20 mg/kg) abolished the protective plateau, or ceiling effect, commonly observed with ascending buprenorphine doses (0.03, 0.1, 0.3 mg/kg, i.v.) on respiration (see Walsh et al., 1994 for more about the ceiling effects of buprenorphine). In this same study, diazepam pretreatment potentiated the dose-dependent inhibition of respiration seen with increasing methadone doses (0.1, 0.3, 1.0 mg/kg, i.v.; see also similar findings by McCormick et al., 1984 and Borron et al., 2002). Since benzodiazepines can have respiratory depressant effects, dependent upon the dose and route of administration, it has yet to be determined if BZDs are acting to potentiate this effect of opioids or simply acting in an additive fashion to depress ventilation (Carraro et al., 2009; Mak et al., 1993; Zacharias et al., 1996). More studies are warranted to help explain the pharmacologic interaction that may occur with BZDs and buprenorphine, as well as other opioids.

In one of the few clinical studies investigating this interaction, patients undergoing anesthesia were administered lorazepam with either fentanyl or buprenorphine. Of 88 patients enrolled, respiratory depression requiring manual ventilation developed in 11 of the subjects. All of these 11 participants had received buprenorphine (Faroqui et al., 1983). More recent, clinical research has only utilized lower doses within the therapeutic range (diazepam 0, 10, 20mg), and therefore has not been able to substantiate these findings (Lintzeris et al. 2006). Nevertheless, prolonged respiratory depression following medical use of opioids in combination with BZDs has been observed by anesthesiologists since the 1980's (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 suggested 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). Nearly half of all heroin users report at least one non-fatal overdose (Pollini et al., 2006), with BZDs being 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 have overdose risk, particularly full agonists like methadone. A recent retrospective analysis of drugs interactions and adverse events among 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 identified 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).

Though the overdose risk for buprenorphine is low, this risk increases when buprenorphine is injected and used in combination with other sedatives (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 commonly used as treatment for opioid dependence and human laboratory studies of combination opioid and BZD use are limited. One study by Reynaud et al. (1998) reviewed post-mortem analysis of opioid dependent individuals. Urine, blood and tissue samples were analyzed and indicated no other medications were taken that could have contributed to the deaths except buprenorphine and a BZD drug.

Another complication of opioid and BZD combined use is the antidotal treatment of acute overdose or over-intoxication. Naloxone is well known for the treatment of opioid overdose. In an effort to reduce opioid overdose deaths, programs have been implemented in parts of Australia, the U.S. and the U.K., where non-medical persons are prescribed naloxone to administer in suspected cases of opioid overdose. The concomitant use of BZDs by the opioid users, who these programs target, may make it more difficult for typically prescribed doses of naloxone to reverse respiratory depression.

We know that naloxone is effective at treating opioid overdose, but are unsure of how concomitant BZD use may alter this. Yet there are preclinical data to suggest that naloxone might directly benefit the treatment of BZD over-intoxication as well (Dingledine et al., 1978; Soubree' et al., 1980). One retrospective analysis found that the addition of between 0.2 and 1.0 mg of flumazenil (a GABA_A receptor antagonist) to low doses of naloxone (0.4-0.8 mg) improved the mental functioning in patients following cases of buprenorphine overdose where BZDs were co-ingested (Me'garbane et al., 2010). Though there is caution in the use of flumazenil due to the risk of seizures and requirement of close monitoring during administration; this data suggests that flumazenil and naloxone may serve as an antidotal treatment in cases of benzodiazepine and opioid overdose.

There are no prospective human studies that assess how the co-use of BZDs may alter the effectiveness of naloxone to reverse opioid overdose. More clinical data is also needed to evaluate novel treatment approaches that utilize naloxone for BZD over-intoxication. In either case, naloxone is an interesting and important consideration in the treatment of opioid and BZD co-abuse.

In addition to the ability to exacerbate drug-related harm, opioid and BZD co-abuse is further complicated by the possibility of opioid and BZD physical dependence and withdrawal (Puntillo et al., 1997). Clinical indicators of opioid withdrawal include: abdominal cramps, diarrhea, bone and muscle pain, insomnia and anxiety (Herridge and Gold, 1988). Symptoms of benzodiazepine withdrawal include autonomic instability, increased anxiety, fear, dread, agitation, confusion, and panic attack. Abrupt BZD withdrawal can result in fatal refractory seizures (Durbin, 1994). Traditional therapeutic approaches for the treatment of BZD dependence that have been utilized 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 in individuals under agonist maintenance treatments (Weizman et al., 2003). Although this may prove to be a useful treatment modality, physicians and treatment providers may be hesitant to maintain BZD dependency because of the risks described above and lack of evidence-based

justification. In either case, studies that focus on polydrug detoxification are scarce and the effectiveness of these strategies has not been investigated extensively.

To further complicate the treatment prognosis for this population, studies have found that when compared to individuals who only abuse opioids, BZD and opioid polydrug abusers: have been using opioids for a significantly longer period of time, 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 patients maintained on methadone, those who were regular BZD users received higher daily methadone doses and abused alcohol more frequently. Similarly, a study by Ross and Darke (2000) found that, compared to those who did not have a lifetime diagnosis of BZD dependence, heroin users with a diagnosis of dependence on BZDs at some point in their lifetime, were more likely to have had a diagnosis of alcohol dependence (83% vs. 60%) and cocaine dependence (23% vs. 4%). In light of these findings, it is not surprising that research has revealed a poorer treatment outcome for these polydrug abusers. Although it has not been shown to alter retention in methadone treatment, BZD use during methadone maintenance is associated with poorer treatment outcomes with respect to general health, legal problems, and alcohol use (Brands et al., 2008; Eiroa-Orosa et al., 2010).

The exacerbated negative factors associated with BZD and opioid polydrug use extends to psychological variables as well. When compared to a control group of heroin users, heroin users who were physically dependent on BZDs were much more likely to be using anti-depressants daily, and more likely to have described a past period of depression including self-harm ideation (Rooney et al., 1999). Other studies have also noted increased frequency of psychiatric comorbidity among this population. Studies have shown that opioid users who regularly use BZDs were nearly 3 times as likely to have had a psychiatric hospitalization during the preceding year. They are also nearly 2 times more likely to have been prescribed medication for emotional problems, and have a much poorer psychiatric status (Eiroa-Orosa et al., 2010). Additional investigations have noted higher frequency 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 behaviors associated with increased risk of contracting HIV and Hepatitis C (HCV) such as: injecting more frequently, sharing injecting equipment more often 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 abusers 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 patients who regularly use BZDs with those who do not. In contrast, Bleich et al., (1999) found significantly increased rates of HCV in a cohort of methadone patients who also abused BZDs. Although research has shown that polysubstance abuse typically increases rates of HCV and HIV infection, more data is needed to specifically assess the impact of combined BZD use on rates of infectious disease transmission among opioid abusers (Backmund et al., 2005, Nurutdinova et al., 2011).

7. CONCLUSIONS

Abundant evidence documents the significant co-use of BZDs and opioids. Opioids have considerable therapeutic utility yet their euphoric effects make them among the most commonly abused drugs in the world. In comparison to opioids, BZDs are believed to act as euphorants in very limited settings and when administered alone, have less abuse liability. Drug users appear to have discovered that BZDs are able to enhance the positive subjective effects of opioids. As such, individuals may be combining opioids and BZDs in order to

achieve a greater level of euphoria. More clinical studies are needed investigating these hypotheses in controlled, laboratory settings.

Individuals in opioid-substitution therapy around the world appear to be particularly vulnerable to opioid and BZD co-abuse. It appears as though 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”. Additional research is needed to elucidate the increased abuse potential of this drug combination. Do BZDs potentiate the reinforcing effects of opioids? Or is the increased abuse liability simply an additive effect of combining two reinforcing drugs?

Individuals with chronic pain who use prescription opioids may be co-using BZDs to increase the euphoric effects of their opioids. Anecdotal reports from users and clinical data showing that these individuals are not using therapeutic doses indicate that BZD use among these individuals is primarily recreational. However, the possibility remains that prescription opioid users are self-medicating insufficient pain management, or co-occurring mood or anxiety disorders. These types of conditions, which BZDs are efficacious at treating, are common among heroin users. Studies investigating the prevalence of affective and anxiety disorders among prescription opioid and BZD co-users may allow us to determine if their concomitant use is recreational or therapeutic.

Future studies should also seek to determine how these individuals are obtaining BZD medications. There is an abundance of research showing the number of ways that individuals obtain prescription opioids. Opioid abusers often: forge prescriptions, obtain opioids from friends and family, visit emergency rooms with complaints of pain, or purchase opioids off the street (Ballantyne and LaForge, 2007; Fishbain et al., 1992). This knowledge of narcotic abuse liability has raised awareness among healthcare professionals; hence more caution is needed when considering patients for opioid therapy. Research has shown that BZDs are the most frequently sold controlled prescription drug on the internet, with 89% of these sites selling this medication with no prescription requirements (National Center on Addiction and Substance Abuse at Columbia University, 2006). This study also found that 70% of those sites requiring a prescription permitted the prescription to be faxed, allowing for the possibility of individuals forging or modifying prescriptions, or sending the same prescription to multiple sites. There has also been a trend towards online consultation in lieu of a prescription. In this case, the consumer completes an online questionnaire that is reportedly evaluated by a physician affiliated with the online pharmacy. Less is known regarding the prevalence of illegal street sales of BZDs. A high incidence of questionable internet “prescribing” and street sales may suggest the need for more stringent national policies regulating availability of these drugs. On the other hand, if BZDs are being obtained primarily through physicians, it may suggest the need for increased vigilance by doctors.

There is still much unknown about the interactions between opioids and BZDs. Although BZDs are a widely used practice for treatment of anxiety disorders, efforts must be taken to prevent the potentially lethal interaction that can occur when opioids and BZDs are administered simultaneously. Benzodiazepines have been shown to eliminate the protective ceiling effect of buprenorphine on respiratory depression, an important benefit of this treatment. Among opioid using populations, physicians may want to consider medications that are not central nervous system depressants, such as low toxicity antidepressants (i.e. SSRIs), atypical antipsychotics, or buspirone in lieu of BZDs. Also, non-pharmacotherapies such as imagery, distraction, meditation, and desensitization could be considered as initial or adjunct management for anxiety disorders.

This review also raises important questions concerning how to treat individuals co-abusing these two drugs. This issue is complicated by the possibility of dual physical dependence upon opioids and BZDs among these individuals. More research is needed on the safety and utility of BZD maintenance strategies, although they may not prove to be a viable treatment approach. Future studies investigating administration of the opioid antagonist naloxone may prove useful in the treatment of combination BZD and opioid overdose.

When used together, the combination of opioid and BZD drugs has serious detrimental effects upon physical health, mental health, and sobriety. In addition to increasing risk of overdose, BZD and opioid polydrug use may exacerbate criminal, psychological and medical problems commonly seen among drug users. As such, we encourage vigilance among prescribers in observing for abusing patterns of use among patients being provided one or both types of medications. Drug treatment centers should also warn users concerning the risks of this drug combination, and encourage treatment for the abuse of both drugs.

Acknowledgments

Role of the Funding Source

Financial support for the preparation of this manuscript was provided by the U.S. National Institute on Drug Abuse (DA030446-01A, DA09236, DA016759, DA022222, and DA031022). However, the sponsor had no role in the decision to submit or writing of this report.

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Table 1

Clinical Investigations of the Interactions between Opioids and Benzodiazepines

Author(s)	Drugs and Doses	n	Outcome
Pond et al., 1982	<ul style="list-style-type: none"> Diazepam: ≈ 0.3 mg/kg for 9 days. Methadone: 50 mg \pm 17 	4	Diazepam failed to inhibit the metabolism of methadone.
Farqui et al., 1983	<ul style="list-style-type: none"> Diazepam: 200 μg/kg Buprenorphine: 2 μg/kg Buprenorphine: 3 μg/kg Fentanyl: 1.5 μg/kg 	88	Eleven patient who had received buprenorphine suffered sudden respiratory depression requiring manual ventilation of their lungs followed by doxaprain infusion.
Preston et al., 1984	<ul style="list-style-type: none"> Diazepam: 20, 40mg Methadone: 50 or 60 mg (mean = 56 mg), 100%, 150% and 200% of normal dose. 	5	The pupil constriction induced by diazepam + methadone combinations was greater than that induced by comparable doses of methadone alone. Diazepam 40 mg significantly increased opioid subjective effects when compared to either drug alone.
Preston et al., 1986	<ul style="list-style-type: none"> Diazepam: 20, 40 mg Methadone: 50 or 60 mg (mean = 56 mg), 100% and 150% of normal dose. 	5	No evidence of a pharmacokinetic interaction between methadone and diazepam.
Farre et al., 1998	<ul style="list-style-type: none"> Flunitrazepam: 1, 2, 4 mg Triazolam: 0.5, 0.75 mg Methadone: 40-50 mg (mean= 44 mg) 	10	Flunitrazepam (4 mg) produced significantly increased ratings of "high" and "euphoria," indicating that the drug had significant abuse liability among methadone-maintenance patients.
Spiga et al., 2001	<ul style="list-style-type: none"> Diazepam: 0, 5, 10, or 20 mg/70 kg Methadone: 80 mg 	5	The 10 and 20 mg diazepam doses significantly increased subjective reports of "good," "like," "strong," and "high." Pretreatment with these doses significantly decreased methadone self-administration.
Lintzeris et al., 2006	<ul style="list-style-type: none"> Diazepam: 0, 10, 20 mg Methadone: 35–100 mg (mean = 55 mg) Buprenorphine: 6–16 mg (mean = 10.5 mg) 	16	Co-administration of diazepam (10 and 20 mg) resulted in greater sedation and strength of drug effects for both methadone and buprenorphine, but had minimal impact on physiological parameters.
Lintzeris et al., 2007	<ul style="list-style-type: none"> Diazepam: 0, 40 mg Methadone: 50–100 mg (mean= 68.8 mg), 100% and 150% of normal dose Buprenorphine: 8–16 mg (mean= 11.1 mg), 100% and 150% of normal dose 	12	Diazepam 40 mg increased the intensity of subjective drug effects (strength of drug effect, sedation) and decreased psychological performance (reaction time, DSST) for both methadone and buprenorphine (independent of the opioid dose).
Zacny et al., 2012	<ul style="list-style-type: none"> Alprazolam: 0.5 mg Oxycodone: 10 mg 	20	The two drugs in combination produced stronger psychomotor effects and performance impairment. Yet, alprazolam did not alter abuse liability-related subjective effects of oxycodone.