Designer benzodiazepines: new challenges and treatment options

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Designer benzodiazepines: new challenges and treatment options

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Introduction

New Psychoactive Substance (NPS) benzodiazepines (AKA designer benzodiazepines) emerged in Europe around 2007, but were first detected and identified in death cases in 2010 in the USA (Bailey et al. 2010) and 2011 in the UK (Maskell et al. 2011a). Since the first NPS benzodiazepines emerged another 20 are being monitored by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), leading to concern that the abuse of NPS benzodiazepines may become a significant global problem. This chapter looks at NPS benzodiazepines, their pharmacology, potency, prevalence, use, abuse, potential poly-pharmacy, risk of hospitalisation, detection in the clinical setting and finally treatment of overdose.

Benzodiazepines

Benzodiazepines are a group of sedative/hypnotic drugs that share a common mechanism of action via the gamma-aminobutyric acid receptor type A (GABA-A) receptor. The benzodiazepines allosterically enhance the effects of GABA, the main inhibitory neurotransmitter in the central nervous system of mammals to diminish the change of nervous transmission occurring (Stahl 2013). These compounds are named benzodiazepines due to their similar chemical structure consisting of a diazepine ring fused to a benzine ring (see figure 1). Traditionally benzodiazepines have been classified either according to their chemistry, duration of action or their half-life (t½) (Drummer & Odell 2001). The most common benzodiazepines based on chemistry are 1,4-benzodiazepines such as diazepam (figure 1A) followed by the triazolobenzodiazepines , such as Bromazolam (figure 1B) (Manchester et al. 2017). Further structural classifications are discussed by Manchester *et al.* (Manchester et al. 2017) and are minor, though important groupings. When looking at the duration of action benzodiazepines with a duration of action of <24 h are classed as short acting and > 24h long acting. The final classification, elimination half-life (t½) is divided into 4 groups ultra-short (<4 h), short (~6 h), intermediate (6-24 h) and long (>24 h), the actual clinical duration of action can actually be increased due the metabolites of the parent benzodiazepines, that are also in many cases pharmacologically active, exhibit longer t½ than the parent compounds (Baselt 2014). When abused users of course don't use generic of trade names for drugs with many "street names" for benzodiazepines such as "vallies", "jellies", "blues", "benzos" in the UK (Anon n.d.) and "stupefy", "tranx", "qual", "heavenly blues", "valley girl", "goofballs", "moggies", "candy", Z bars", "sleepers", school bus" and "dead flower powers" in the USA

(Anon n.d.). The original street name back in the 1960's when first released was "mother's little helper(s)" as referenced in the song of the same name by the Rolling Stones in 1966.

History and prevalence of the use of Benzodiazepines

Benzodiazepines were introduced into clinical use in 1960 with chlordiazepoxide (Librium), closely followed in 1963 with the release of probably the most well know benzodiazepine, diazepam (Valium) (Schütz 1982). The introduction of benzodiazepines lead to a revolution in the treatment of anxiety and insomnia as they exhibited an increased therapeutic index and thus safety when compared to the barbiturates, the drug class they replaced (Woods et al. 1992) reducing the number of deaths that were seen with the use of barbiturates. Benzodiazepines are not only used for the treatment of anxiety and insomnia but also for the treatment of muscle spasm, tetanus and as anti-convulsant (Anon 2018a). The safety and efficacy of benzodiazepines led them to being the most prescribed group of drugs in the world with around 3.4 ± 4.15 % (mean ± SD) of people between the age of 15 - 64 around the world using tranquilisers and sedatives based on United Nation Office of Drugs and Crime (UNODC) data from 2015 (Anon 2018b). There is a gender split of the use of tranquilisers and sedatives, of which benzodiazepines are the major group, with on average greater worldwide use by women (5.06 ± 9.18 %) compared to men (3.00 ± 3.34 %). Further data on the prevalence of benzodiazepine use around the world comes from the International Narcotics Control Board (INCB) a united nations (UN) agency. The INCB uses a defined daily dose for statistical purposes (S-DDD) in order to determine not only the amount of a drug manufactured around the world but also the amount that is being consumed (Anon 2016). In 2015, the last year of available data, 27.9 billion S-DDD of benzodiazepines were manufactured, up 53% from 2014 (Anon 2016). The top 3 prescription drugs manufactured were alprazolam (53.6 %), lorazepam (17.6 %) and diazepam (14.6 %). The global consumption of benzodiazepines was 27 billion S-DDD (Anon 2016). The top five countries consuming benzodiazepines are USA (9 billion S-DDD), France (1.9 Billion S-DDD), Brazil (1.7 billion S-DDD), Spain (981 million S-DDD) and Italy (930 million S-DDD). However when calculated as S-DDD per 1,000 inhabitants the countries that consume the highest amount of benzodiazepines are Finland (865 S-DDD), Ireland (427 S-DDD) and Belgium (134 S-DDD) (Anon 2016) these data show the increasing use and manufacture of benzodiazepines around the world. This increasing use of benzodiazepine is not always legitimate use with abuse of benzodiazepines being a significant problem around the world.

Abuse of Benzodiazepines

The abuse of benzodiazepines was recognised quickly after their release onto the market in 1961. Due to their recognised abuse, in 1971 33 benzodiazepines were placed under control by the UN convention on Psychotropic Substances, this has risen to 36 recently due to the emergence of NPS benzodiazepines (International Narcotics Control Board (INCB) 2016). Studies into the abuse of benzodiazepines have suggested that they are used to get high, alleviate stress or to help with sleep (Kapil et al. 2014) when used with other drugs such as opioids, benzodiazepines are abused to reduce the withdrawal effects of the opioids and to enhance or prolong the effects of the concomitantly used drug of abuse (Vogel et al. 2013).

The source for abused benzodiazepines has changed over time. Before 2007 benzodiazepines were diverted from both legal sources (false prescriptions, pharmacies) and also illicitly manufactured, but the illicit use of benzodiazepines were benzodiazepines that were available for prescription in that country (Ibañez et al. 2013). In 2010 however the USA (Bailey et al. 2010) and the UK in 2011 (Maskell et al. 2011b), started to detected phenazepam in drug related deaths (DRD), a drug that was at that time only available for prescribing in the former soviet states. Phenazepam as well as nimetazepam were also detected a few years earlier in Europe in 2007 (Drugs 2013) as being detected in seizures by customs and law enforcement agencies in Europe but at the time there had been now cases of detection in human samples either clinical or post-mortem. These detections were the start of the rise of what are now termed new psychoactive substances (NPS) (also known as "legal highs", "designer drugs" and "bath salts") throughout the world. This rise of NPS have been particularly prevalent in Europe where the EMCDDA via the European Early Warning System (EU EWS) is now monitoring over 620 substances, with 20 of these being benzodiazepines (European Monitoring Centre for Drugs and Drug Addiction 2017). As can be seen in table 1 there has been a small but increasing trend in the detection of "new" benzodiazepines being reported to the EMCDDA each year (European Monitoring Centre for Drugs and Drug Addiction 2017). Leading the UN to consider the non-medical use of benzodiazepines as a "growing threat to public health" (Lobal et al. n.d.). The rise of the use of chemical compounds that have physiological and psychological effects but have not been properly tested in clinical trials like licenced medicines is worrying from both a social and medical angle with the drugs having unknown dangers.

NPS Benzodiazepines (Designer Benzodiazepines)

The rise of NPS benzodiazepines was initially an abuse of drugs that were available only on prescription in certain parts of the word. Phenazepam (Russia) and etizolam (Japan) being the first (Manchester et al. 2017). As these drugs were not controlled under many countries legislation at that time, this allowed to avoid drug legislation, and any legal penalties (as long as they were marketed as "not for human consumption" and not marketed or sold as medications). So were attractive to users and suppliers. National legislation quickly caught up with this "trick" and so began the "cat and mouse" game. Suppliers would bring out a new compound that had similar pharmacological properties to the banned substance but which was not covered by national legislation thus allowing them to "market" the compound, the relevant government would detect them control the substance and so the cycle would begin again. The "development" of new NPS benzodiazepines to avoid legislation was made easier due to the large drug libraries, published literature and patents of the various drug companies. The synthesis and development of new benzodiazepines in the 1960's to 1990's lead to an estimated 3000 (or more) benzodiazepines (Anon n.d.) allowing a wide variety of "new" compounds to be produced as NPS. The first NPS benzodiazepine to appear on the market that was not a prescription drug was Pyrazolam in 2012 (Anon 2012) a compound that was patented in 1979 (Manchester et al. 2017), since then to date a further 21 benzodiazepines have been detected by drug early warning systems in Europe and around the world (European Monitoring Centre for Drugs and Drug Addiction 2017) and it is expected that these will not be the last of the NPS benzodiazepines that will emerge. Legislation around the world has attempted to stop the "cat and mouse" of NPS with the Novel Psychoactive Substances Act (2016) in the UK, making it illegal to supply or import a drug that is "psychoactive" or the Psychoactive Substances Act

(2013) in New Zealand in which the seller of any "psychoactive substance" must prove it is "low risk" before being able to sell it. The long-term impact of this legislation is yet to be seen and maybe difficult to interpret due to the change of how these drugs are sourced by users particularly the move "underground". In 2011 "silk road" was set up on the "darknet" where users and vendors were able to use the internet to buy and sell NPS but remain anonymous as their IP addresses are hidden. The development of Crypto currencies such as bitcoin also allow users to pay for the NPS anonymously, increasing the problems for law enforcement agencies. The problem of darknet sales is illustrated by the 2017 global drug survey that found of the people in the countries that responded to the survey between 1.4% (Iceland) and 41.4% (Finland) of people obtained drugs from the darknet. The hot spots for purchase of drugs on the darknet are Europe and the USA (Winstock et al. 2017). This increases the problem of determining the use and abuse of NPS, but also controlling the problem of NPS abuse.

Pharmacology of NPS Benzodiazepines

As a majority of the NPS benzodiazepines around the world are "orphan" compounds there is a limited amount of knowledge on the pharmacology, toxicology and pharmacogenetics of these compounds. This may mean that the compounds could have not only serious acute medical effects but also acute and/or chronic psychological effects. In the clinical environment benzodiazepines are commonly administered via the oral, intravenous, intramuscular or rectal routes depending on their desired effect (Anon 2018a). Due to these routes of administration they are found in different formulations such as tablets, capsules, solution or emulsion for injection, oral suspension or solution and enema solutions (Anon 2018a). When used illicitly similar routes of administrations are used with oral, intravenous, rectal and sublingual being reported as being "successful", at least with flubromazepam (Andersson & Kjellgren 2017). There have also been reports of people attempting to "Vape" and smoke benzodiazepines again with reports of these routes "successfully working" (Winstock et al. 2017; Andersson & Kjellgren 2017). On the market the NPS benzodiazepines have been sold in tablet, capsule and powder formulations (European Monitoring Centre for Drugs and Drug Addiction 2017). Due to the abuse of NPS there is a concerted effect by the scientific community to understand the clinical effects, pharmacology, pharmacokinetics and identification of NPS in human body fluids and tissues. The initial work on detection had scientific study has been focused on the metabolism and basic pharmacology of NPS benzodiazepines due to a difficulty in carrying out clinical studies around the world. Benzodiazepines follow predictable metabolism routes that have been know about for licenced benzodiazepines (Phase I – hydroxylation, reduction, acetylation, demethylation, ring cleavage; Phase II – glucuronidation) with the exact metabolic pathways depending on the function group present. The NPS metabolic pathways that have been elucidated have been shown to follow these models and allow prediction of metabolites when new NPS benzodiazepines are identified. Manchester *et al.* review the various metabolites and metabolic pathways (Manchester et al. 2017). Benzodiazepines are mainly metabolised by CYP3A4, although other CYP enzymes (such as CYP3A5, CYP2C19, CYP2B6, CYP2C18, and CYP2C9) are involved (Fukasawa et al. 2005; Fukasawa et al. 2007; Mizuno et al. 2009). To date only CYP2C19 polymorphisms have shown to influence elimination t½ of benzodiazepines to any clinical effect with t½ being doubled in one case of a CYP2C19 poor metaboliser (Bertilsson et al. 1989; Goldstein 2001; Fukasawa et al. 2007; Fukasawa et al. 2005).

As previously discussed the duration of action of benzodiazepines can be significantly increased by the production of active metabolites that will commonly have a duration of action longer than their parent compounds. Metabolites such as nordiazepam (metabolite of diazepam) and desalkylflurazepam (metabolite of flurazepam) can exhibit t½ of over 100 h even up to 144 h (Smith et al. 1979; Breimer & Jochemsen 1983; Mandelli et al. 1978) leading to drug effects lasting for a significant proportion of time. An example of this was illustrated when 61 cases of phenazepam consumption in Sweden reported 23% of patients experiencing side-effects for up to 5 days after ingestion, in some cases CNS depression lasted for as long as 3 weeks (Luzhnikov et al. 2010). A number of the NPS benzodiazepines that have been detected are active metabolites of already known benzodiazepines (Katselou et al. 2017) and it is likely that this trend will continue. The known t½ and volume of distribution (V_d) of the current NPS benzodiazepines are given in table 2. Due to the lack of clinical studies to date there is no data on the bioavailability or plasma protein binding of the NPS benzodiazepines, however it would be expected that they would be in a similar range of the currently licenced benzodiazepines, 44 - 96 % oral bioavailability and 70 - 97% plasma protein binding (Manchester et al. 2017).

The pharmacodynamics/pharmacokinetics and the exact dose of individual NPS benzodiazepines are very difficult to predict as is the potency or effects of the individual benzodiazepines. The majority of the NPS benzodiazepines are illicitly manufactured and dosing information on any covered material may be unreliable. Analysis of illicit tablet of diazepam and "erimin 5" (nimetazepam) tablets, found that the diazepam tablets although labelled as 10 mg contained anywhere between 0 and 48 mg of diazepam and that the "erimin 5" tablets rather than containing nimetazepam contained phenazepam (Lim et al. 2017). There have also been numerous other cases around the world of illicit and fake diazepam tablets either not containing the claimed active ingredient or the active ingredient is a different dose than claimed (Lobal et al. n.d.). The clinical effects of NPS benzodiazepines are likely to be down the individual potency however this is not easy to determine.

Potency of NPS benzodiazepines

The lack of pharmacological testing of the NPS benzodiazepines to date either using functional *in vitro* testing or *in vivo* has made it difficult to determine the potency of the NPS benzodiazepines. Quantitative structure activity relationship (QSAR) that relates the structure of the molecules to biological activity using a known model allows some initial prediction of potency. Triazolobenzodiazepines (such as etizolam) are generally more potent than 1,4-benzodiazepines (such as diazepam) although individual potency will depend on the functional groups present (Hester Jr. et al. 1971; Meguro & Kuwada 1970) so does not allow more that a rudimentary determination of the potency. Recent work by Waters *et al.* has developed a QSAR model to determine biological activity of NPS benzodiazepines (Waters et al. 2018) that show the strength of binding of the drugs to the GABA-A receptor but not the pharmacological potency. The best current method to develop some idea of the potency of the NPS benzodiazepines is to look at the common "dose" of NPS benzodiazepines taken by users. The scale being that the most potent drugs (+++++) to the least potent drugs (+) table 3, with the potency of the individual NPS benzodiazepines shown in table 2. This assumes that the common dose of the drug gives a similar level of "effect" in an individual; which may not be

true. To give an idea of the potency, diazepam would score (+/++) where as clonazolam, flubromazolam and flunitrazolam would be the most potent drugs (+++++) correlating with user reports (Huppertz et al. 2018; Anon n.d.; Theis n.d.; Andersson & Kjellgren 2017). Due to the very low dose (~0.5 mg) that is needed for these drugs it is possible that the user may easily overdose due to the difficulty in measuring the dose if using the powder form. If taking tablets, as the "quality control" of the illicit manufactures is poor it is highly likely the use will take a dose that they did not intent too. The NPS benzodiazepines are however the NPS grouping that have the lowest risk of fatal toxicity of the NPS compounds this should however not be taken as that they are safe compounds to take (King & Corkery 2018).

Effects and side effects of NPS benzodiazepines

Benzodiazepines, due to their high therapeutic index are considered to be safe in overdose, at least when they are taken alone (3). Benzodiazepines are however addictive and users become rapidly tolerant to their effects (Seldenrijk et al. 2017). Side effects encountered by the users in both the therapeutic and illicit setting include drowsiness, ataxia, dysarthria, nystagmus, and occasionally respiratory depression, and coma (Anon 2018a). With intravenous administration of benzodiazepines thrombophlebitis and venous thrombosis can also occur (Anon 2018a). One clinical report suggests that benzodiazepines at normal intravenous doses may cause pro-arrhythmic and anti-arrhythmic effects in susceptible patients (52). Benzodiazepines however, are not considered as having a risk for the induction of cardiac arrhythmia by the US federal drug administration, Micromedex (independent medical database) or UK Toxbase at therapeutic doses (53). There have been reports in the literature that NPS benzodiazepines may cause tachycardia and bradycardia in acute overdose (Maskell et al. 2012; Lukasik-Glebocka et al. 2016) and benzodiazepine overdose has been associated with atrioventricular block (Arroyo Plasencia et al. 2012). Suggesting that clinicians should not rule out possible cardiovascular effects in eith normal use or overdose. Due to their addictive nature it is not recommended to prescribe benzodiazepines for more than 4 weeks although studies have shown that they are prescribed for months or even years (Ford et al. 2014). Regular benzodiazepine users can suffer from severe physiological (pain, tension, spasm, tachycardia, seizure) and psychological symptoms (anxiety, depression, insomnia and depersonalisation) if the benzodiazepine treatment is ceased abruptly (Ashton 2005; Barker et al. 2005), with 30 - 40% of patients suffering from severe withdrawal symptoms even after a month (Anon n.d.; Lader & Russell 1993), with these effects expected to be observed with long term NPS benzodiazepine abuse. Users of benzodiazepines can often suffer from memory impairment and amnesia, with longer term users suffering from long-term cognitive effects (Barker et al. 2004), there is also evidence of depression and emotional blunting in long term users (Ashton 1987). Paradoxical reactions (such as aggression, increased talkativeness, excitement, excessive movement and loss of inhibition) are also observed in around 1% of benzodiazepine users with different paradoxical reactions observed with different benzodiazepines (Mancuso et al. 2004).

Due to the lack of clinical studies of NPS benzodiazepines there are limited resources for information about the effects and side effects of NPS benzodiazepines. The "best" current resource on information on the effects of NPS benzodiazepines are the large variety of internet forums (i.e. bluelight.ru, flashback.org) where users discuss what substances they have taken

and the effects/side effects they have experienced. It is important to note however that the users may have not taken the drug or the dose they think they have and, in some cases, may be under the influence of multiple drugs. A summary of the user reports on the effects is given by Manchester *et al.,* (Manchester et al. 2017). In summary the experiences are similar to those of prescription benzodiazepines just to different degrees including anxiolytic, sedating, euphoric and in some cases causing amnesia and blackouts over a few days (Manchester et al. 2017). The experiences of one of the most potent NPS benzodiazepines flubromazolam (+++++ on our scale) has been explored in more detail with users reporting heavy hypnotic and sedative effects, long lasting amnesiac effects and in some cases euphoria, intense wellbeing and loss of control. There were cases of acute psychiatric reactions and arrest by the police due to behaviour (Andersson & Kjellgren 2017). Users also reported raised tolerance and serve withdrawal (Andersson & Kjellgren 2017). In a clinical study of severe intoxication of flubromazolam, the intoxication was associated with coma, hypotension and rhabdmyolsis (Lukasik-Glebocka et al. 2016). The exacerbated effects and withdrawal appear to mirror the suspected potency of flubromazolam and suggest that the more potent NPS benzodiazepines are likely to have more severe and exacerbated side effects and withdrawal compared to prescription benzodiazepines and this should be taken into account when treating NPS benzodiazepine intoxication/overdose and when withdrawing users how have been abusing long term.

Frequency of NPS benzodiazepine use

The scale of the problem of NPS benzodiazepine can be estimated from data collected by both the Global Drug Survey (GDS) and the European Union – Early Warning System (EU-EWS). To date the lifetime, use of NPS benzodiazepines is 2.5%. With only 1.3 % of respondents using NPS benzodiazepines in the last year (2017) (Winstock et al. 2017). In the EU the EU-EWS reported in 2015, the last year that data is available for, that 11% of NPS seizures were benzodiazepines the third largest group (behind cathinones and Synthetic Cannabinoid Receptor Agonists (SCRA)) (Winstock et al. 2017). Since 2011 the number of countries reporting the detection of NPS benzodiazepines has increase from 3 (in 2011) to 21 (2015) (European Monitoring Centre for Drugs and Drug Addiction 2017).

The demographics of NPS users around the world from surveys suggests that they are generally male (60 - 80%) with a median age of around 25 years old (Winstock et al. 2017; Soussan & Kjellgren 2016), females tend to be slightly older (mean ~30 years) than males (mean ~27 years) (Soussan & Kjellgren 2016) however the mode for both genders was 18 (Soussan & Kjellgren 2016; Soussan et al. 2018) the high median age is probably due the wide age range of people taking NPS (18-75 years). Over the past 5 years ~30% had used nine or more NPS (Soussan & Kjellgren 2016). In study from 2016 etizolam was in the top 5 most frequently used NPS substances with 76% of users planning on using etizolam again (Soussan & Kjellgren 2016), users were also at that time using flubromazepam and diazepam. The users main reason for abusing benzodiazepines was “coping with life challenges” and also as a social facilitator (Soussan & Kjellgren 2016). The true picture of NPS benzodiazepine use and abuse around the world is hard to determine but it is certainly growing.

Polypharmacy of Benzodiazepines

Apart from recreational use, Benzodiazepines are also commonly co-ingested by other groups of drug users particularly high-risk opioid users[1], with an estimated 38-75% of high risk opioid users abusing benzodiazepines (Heikman et al. 2017; Jones et al. 2012). The combination of benzodiazepines with opioids potentiates the clinical features seen, including extreme sleepiness and risk of overdose (Park et al. 2015). This concomitant abuse of benzodiazepines is of particular concern as this increases the risk of non-fatal and fatal overdose, particularly due to respiratory depression (White & Irvine 1999). Around the world benzodiazepines were identified in between 40% and 80% of opioid related deaths showing the increased risk of abuse of opioids and benzodiazepines (EMCDDA n.d.). For licenced benzodiazepines it has been estimated from a study in the USA that in unintentional deaths involving benzodiazepines only 46% of the users had a valid prescription (Toblin et al. 2010). Opioid users are abusing NPS benzodiazepines as well as licenced benzodiazepines for example data from Scotland in 2016 etizolam, diclazepam and phenazepam were detected in opioid deaths (Anon 2017). Showing that clinicians need to be aware of other drugs in any potential "benzodiazepine" overdose. The added complexity is that high-risk opioid users tend to use supra-therapeutic or 'mega doses' of benzodiazepines significantly above those prescribed. 40 to 150 mg of oral/intravenous temazepam and/or diazepam concentrations have been reported (Jones et al. 2012; Stitzer et al. 1981; Robertson & Ronald 1992). There is a lack of information on the effects of these high doses on pharmacokinetic and pharmacodynamic variables particularly in overdose. In the treatment and determination of NPS benzodiazepine abuse it can be important to determine that NPS benzodiazepines have actually be taken.

Immunoassay detection of NPS Benzodiazepines

Toxicology screening tests for drugs of abuse and therapeutic drugs can be carried out in emergency departments in order to determine if the clinical symptoms observed could be due the use of drugs. The results of these tests can assist in the clinical decision making further down the line. Presumptive tests are often carried out using immunoassay based point-of-care systems from urine samples that can give results within 10 minutes (Lager et al. 2018). The point-of-care testing kits employ targeted screening that will detect drugs in a "drug panel" such as amphetamines, barbiturates, benzodiazepines, cocaine, cannabis (tetrahydrocannabinol (THC) the active chemical), opiates (including methadone and morphine), tricyclic antidepressants (George & Braithwaite 2002; Attema-de Jonge et al. 2012). Immunoassay tests rely on the antibodies reacting with the drug molecule and typically will only identify that a drug from a specific group has been detected (such as an opiate) rather than the specific drug being determined. Immunoassays suffer from false positives, where a positive result will be obtained when there is actually not drug present due to antibody binding to structurally similar compounds. This has been show to occur with benzodiazepines where a study showed that Efavirenz (antiretroviral used in the treatment of HIV/AIDS) cross-reacts to cause a false positive for benzodiazepines (Blank et al. 2009). Another problem with a positive is that depending on the cut-off (the level at which the immunoassay will give a positive for the drug in question) of the immunoassay screen the drug may be detected but at a concentration below

[1] The term 'high-risk drug use'means recurrent drug use that is causing actual harms (negative consequences) to the person (including dependence, but also other health, psychological or social problems) or is placing the person at a high probability/risk of suffering such harms' EMCDDA (www. emcdda.europa.eu/attachements.cfm/att_218205_EN_PDU%20revision.pdf

that which would cause impairment or intoxication which could lead to an incorrect presumption for the cause of symptoms displayed by the patient (Wu et al. 2003). False negative have also been reported as not all benzodiazepine with bind with the antibody and will therefore be undetected on immunoassay (Huppertz et al. 2018; Moosmann et al. 2014; Moosmann et al. 2013). Any definitive identification of the drug(s) concerned should be carried out using a different chemical technique (such as LC-MS/MS or GC-MS) however this confirmation can take days so may not be applicable to a critical case. The cross reactivity observed in immunoassay testing can however be an advantage with NPS benzodiazepines that of course have similar chemical structures to the benzodiazepines (Manchester et al. 2017). As can be seen in table 4 several of the NPS benzodiazepines have been shown to cross react to give positive "benzodiazepine" results allowing a presumptive identification of benzodiazepine use, although for a large number of NPS benzodiazepines no analysis has been carried out. Tablets that are found on the patient may also be identified by using specialist identification services such as Tic-Tac (www.tictac.org.uk) that have visual databased on abuse and illicit NPS tablets. The identification of the substance that has been taken may be of use in clinical treatment, but often supportive therapy is given and no drug identification is needed for successful treatment.

Benzodiazepine presentation in the Emergency Department

Due to the high therapeutic index that licenced benzodiazepines have they are less likely to be fatal in overdoses that only involve a single benzodiazepine. Benzodiazepines however are often taken with other substances such as alcohol, cannabis and opioids or play a part in resulting trauma requiring hospitalisation. NPS benzodiazepines, due to their increased potency compared to licenced benzodiazepines are also more likely to require hospital treatment in overdose. Data from the European Drug Emergencies Network (Euro-DEN Plus), a network of 15 hospitals across 9 EU countries in 2015, reported that of the ~5,000 presentations 75% were males with a median age of 31. This study found that 60% involved a single drug, 27% two agents and the remaining 13% involved 3 to 6 agents (Dines et al. 2015). Licenced Benzodiazepines were the second largest group reported in the study, most commonly associated with opioids. 9% of the presentations involved NPS compounds at that time the data identified mephedrone as the most common NPS (Dines et al. 2015). Australian and US data back up the prevalence of benzodiazepines in overdoses with 54% of people admitting using benzodiazepines in the 24 hours before admittance (Najman et al. 2017). The US data from the Drug Abuse Warning Network (DAWN), has observed an increase in the number of cases of benzodiazepines from 2004 to 2011 (the last year data is available) of the 19% of visits involving sedative-hypnotic drugs 28% involving benzodiazepines alone (Kaufmann et al. 2018) although in this data set the majority of patients were females (64%) with 50% of the patients being over 45 years old. There is a paucity of data on the prevalence of emergency department visits for NPS benzodiazepines. The "best" data comes from the global drug survey where there were higher rates seeking emergency medical treatment for women than men (Winstock et al. 2017). Only 0.5% of users in the survey sought emergency medical treatment for NPS (no data on NPS benzodiazepines) (Winstock et al. 2017). These data suggest that in an emergency setting clinicians are more likely to see benzodiazepines being abused with opioids, these benzodiazepines are likely to be licenced benzodiazepines but there is a rising number of people abusing high potency NPS benzodiazepines (in both the recreational and

opioid using drug populations) and this is likely to see an increase in people seeking emergency medical treatment for acute overdose. Due to the influence of NPS benzodiazepines on behaviour, memory and the ability to drive, there may be an increase in accidents, driving related accidents or the use of NPS in drug facilitated sexual assault.

Acute Hospital Admission

It is important to be able to give appropriate treatment to overdose patients in order for a good clinical outcome. This can however be problematic as people rarely arrive at the emergency department perfectly packaged up with a clear and accurate history, a single perpetrating factor and no contributing health concerns that are all documented. In fact, some people never make it to the hospital in the first place. Scotland has one of the highest rates of drugs deaths in the world (National Records of Scotland 2016) and drug related deaths are a significant cause of early death around the world (European Monitoring Centre for Drugs and Drug Addiction 2017) and a majority of these never reach a hospital for treatment. Around the world the dispensing of naloxone the opioid antagonist to users and friends of users is thought to have helped with a reduction in overdose deaths but the data is unclear (Johnson et al. 2016).

For all acute hospital admission, a clear systematic and structured approach is acted on to mitigate surprises later down the line. This approach not only allows for the systematic gathering of information but also allows for a multi-level rapid team approach, a baseline of patient function highlighting improvement or decline and a checklist aid memoir that covers the key and vital components in each and every patient assessment. One of the most recognised generic, systematic, structured and organised approaches which is recognised around the world is the A-E assessment and is often the basis of teaching various levels of medical care from basic first aid to advanced life support. The A to E approach can also be built on depending on the experience of the practitioner administering the care and allows all levels of practitioners to follow the rational and thinking behind each step for every patient. The initial management of any critically ill patient in the community or to the hospital setting regardless of the precipitating factors will follow this or a similar systematic approach (Resuscitation Council UK 2018b)

All patients attending the Emergency Department come with some level of history either recounted from their own experience or collected from friends, family, witnesses and bystanders or from the emergency service. It can range from as little as the situation in which the person was found to a detailed account and chain of events. Regardless of this information the initial management remains the same however in may well play a key role to later management decisions.

Despite being handed over with a potential clear history of benzodiazepines overdose the initial management will follow the same systematic approach as there is no way of knowing exactly, even with the use of urine immunoassay screening for presumptive identification of drugs, what the person has potentially ingested. Even an identification for an immunoassay will not identify the amount of a substance that has been taken. As discussed above even if the patient "knows" what "dose" they have taken this information may not be correct due to incorrect labelling or manufacture of potential NPS substances. People may provide packets of drugs, pills, paraphernalia etc and give a detailed history of where they were and what they were doing

however a co-existing unknown underlying condition may also co-exist contributing to the clinical presentation.

An initial management of a patient must focus on acute stabilisation of the presenting patient. Once the patient is stable the presenting history, medical history, medications, allergies and a focused physical examination become more important for further management. In terms of overdose presentation management is focused on supportive care, prevention of further absorption, potentially administering an antidote, if the drug taken is positively identified or the antidote would not be expected to cause any further harm to the individual and finally the clinical interventions may potentially focus on aiding elimination of the drug (Hoffman et al. 2014).

Initial Management and primary survey

The A to E assessment is a tool to provide a rapid assessment addressing the most critical aspects systematically (Resuscitation Council UK 2018a).

1) Airway:

Consideration to the mode of air entry is first to be assessed. How is the mouth and nose or is there a tracheostomy present? Does the patient have any airway adjuncts present or have they been intubated? Is there anything that may compromise air entry such as vomitus, blood, lose or fake teeth, debris or swelling? Anything that may comprise air entry needs to be addressed and escalated as required.

2) Breathing:

After assessing the mode of air entry an assessment of air movement and ventilation is required. Assessing active breathing and respiratory rate, symmetrical chest rises and fall or if there is any deviation to one side or paradoxical movement. Assessing whether the chest cavity is dull, hollow or tympanic to percussion. Establishing if there is bilateral air entry and if that air entry is compromised noted by added or absent sound on auscultation. Other investigations into the effectiveness of breathing include a chest X-ray, blood saturation monitoring, arterial blood gas (ABG) monitoring and capnography. When encountering any issue with gas exchange these should be acted on immediately to maximise oxygenation in the acute setting then titrated when appropriate.

3) Circulation:

Non-invasive monitoring can be attached to measure blood pressure, heart rate and heart rhythm via a 3 lead. A formal 12 lead ECG (electrocardiogram) can further assess electrical activity of the heart. Venous access to draw off bloods to assess Full Blood Count (FBC), Urea and electrolytes (U+E), Creatinine, Creatinine Kinase (CK), Glucose, Cardiac Enzymes (troponin), C-reactive proteins (CRP) and liver function test (LFT). Serum alcohol, paracetamol and salicylate levels can also be obtained. Venous access also allows for the intravenous administration of fluids and medications as required. The recording of hourly urine output via a urinary catheter also provides useful information on perfusion, fluid balance and can be taken for biochemical, immunoassay and for microscopy, culture and sensitivity testing.

4) Disability:

Assessment of a patient's neurology looking at pupil size and using AVPU (Alert, responds to Voice, responds to Pain or unresponsive) or the Glasgow coma scale (GCS) can provide a quick level of function and an easily reproducible baseline for comparison. Further focal neurology testing may not be appropriate in the acute setting but revisited later testing tone, power and reflexes.

5) Exposure:

Assessing temperature highlighting hyper or hypothermia, looking for any cuts, fractures or bruises, drug patches, rashes, any documentation or medications on their person.

The primary assessment should provide all the necessary information needed to provide supportive care or escalate if required to more active care such organ support through intubation, ventilation, sedation and cardiovascular support if required. Information obtained through the history and examination can then be further acted on the focus further management.

Clinical manifestation of benzodiazepine overdoses

As discussed before Benzodiazepines have been clinically used since 1960 and sedative-hypnotic agents due to their mode of action on the GABA-A receptor, GABA being the chief inhibitory neurotransmitter of the central nervous system (CNS). They are used to treat anxiety, seizure, withdrawal and insomnia. They are also frequently used clinically in combination with other agents for procedural sedation (Hoffman et al. 2014)

Benzodiazepines are quickly absorbed by the GI tract achieving peak concentration levels in the first 30-90 minutes (Drummer & Odell 2001). They are primarily metabolised hepatically and therefore are affected by other agents that affect the same enzymes of metabolism resulting in an inhibitory or enhancing metabolism (Preston & Stockley 2016). When taken alone Benzodiazepines rarely cause significant toxicology and supportive care in the hospital usually result in full recovery (Hojer et al. 1989). Patients have been known to recovered following ingestion of 500 – 2000 mg of diazepam within a 48hr window (Baselt 2014). As described above non-prescribed intentional ingestions of benzodiazepine however usually involve a co-ingestion such as alcohol or opiates (Hojer et al. 1989) that can enhance the CNS depression effects. As a sedative-hypnotic agent benzodiazepine overdose typically consists of CNS depression with normal vital signs however when co-ingested this can lead onto further organ dysfunction such as respiratory depression and cardiovascular compromise (Hoffman et al. 2014). CNS depression leading to an altered mental state however is a common finding not just drug overdose but in a wide range of medical conditions so it is important to conduct a thorough assessment.

When a drug overdose is suspected toxidromes can be a useful tool to narrow down to suspected substance. The sedative-hypnotic toxidrome is characterised by a depressed mental state, normal vital signs and an unremarkable physical exam (table 5). These expected toxidrome was mirrored in a in a flunitrazepam overdose the patient presented with, presented with deep coma (Glasgow coma scale score 3), bilateral pinpoint unreactive pupils, acute respiratory failure (6 – 8 breaths per minute) and hypotension (blood pressure 80/40), tachycardiac (102 beats/min) (Lukasik-Glebocka et al. 2016).

Treatment of Benzodiazepine overdose

In suspected drug overdose patient's supportive management is the most important aspect of treatment and is often adequate enough to see them through to discharge from hospital. To maximise this, after the initial management to stabilise the patient a more focus approach can be initiated.

Activated charcoal has fallen out of favour in recent times however it may still be considered if a patient present within 1 hr of ingestion (Juurlink 2016). Patient presentation is usually later than 1hr from ingestion and peak plasma concentrations of benzodiazepines are reached within 30-90 minutes. The risk of aspiration and maintaining a patient airway tends to contraindicate activate charcoal however it may still be considered if an additional life threatening co-ingested drug is indicated that will benefit from activated charcoal (Juurlink 2016).

There have been discussions of the use of the GABA-A receptor benzodiazepine antagonist flumazenil in the treatment of benzodiazepine overdose, it is a drug like naloxone that is used as an antidote for opioid overdose, due to it being an opioid receptor antagonist, that has a rapid onset and a short duration of action (Sivilotti 2016). Unlike naloxone that is widely used in the clinical setting the use of Flumazenil differs from country to country. In the United Kingdom Flumazenil is not licenced for the treatment of benzodiazepine overdose (Anon 2018a), despite this NICE guideline suggested that flumazenil should be considered in patients presenting with a benzodiazepine overdose (Excellence 2016) with doses of 0.2 mg (iv) every 1 to 2 minutes, until the reversal of excess sedation or 1 mg total dose (Sivilotti 2016). The concerns with the use of flumazenil are that it may precipitate benzodiazepine withdrawal, inducing seizures and agitation. The other contraindications include a history of epilepsy, co-ingestion of drugs such as tricyclic antidepressants and stimulants as flumazenil lowers the seizure threshold and long term benzodiazepine use due to a risk of withdrawal symptoms. Precise risk estimations for the use of flumezanil have been determined from a large meta-analysis investigating the administration of flumezanil for benzodiazepine overdose in 994 patients (13 different trials). The results suggested that adverse events, mainly agitation and gastrointestinal symptoms, were significantly more common in the flumezanil group than the placebo group (risk ratio 2.85; 95% CI 2.11-3.84), with serious adverse events, supraventricular arrhythmia, convulsions, again significantly more common in the flumezanil group than in the placebo group (risk ratio 3.81; 95% CI 1.28-11.39) (Penninga et al. 2016). The study concluded that flumazenil should not be routinely used and the risk benefits of any administration should be weighed up in each patient. It is important to appreciate that a through history may allow for the safe administration. It is important to note that as flumazenil has shorter t½ than many benzodiazepines, particularly NPS benzodiazepines re-sedation may occur. In the case of flubromazolam overdose in the literature flumezanil was used as an antidote following the positive identification of benzodiazepine use by an immunoassay screen. An improvement in the clinical situation was observed on the administration of flumezanil with GCS improvement from 3 to 10 and spontaneous breathing (the consciousness however deteriorated after 30 minutes presumably due to the short t½ of flumezanil and the long (~10-20h t½) of flubromazolam (Lukasik-Glebocka et al. 2016), in this case noradrenaline (iv central line) was used to increase blood pressure throughout. The patient was moved from the intensive care unit 9 days after admission after supportive ventilation. Full case details can be found in the publication (Lukasik-Glebocka et al. 2016). The indication in the case was that flumezanil was of little apart from confirming the overdose of a benzodiazepine.

As a large number of benzodiazepine overdoses involved opioids naloxone may be administered as an antidote, an this may preclude the use of flumezanil. However, naloxone has been shown to reverse benzodiazepine effects in a number of studies (Solhi et al. 2011; Malizia et al. 1982; Jordan et al. 1980) this is possibly due to its known interactions with the GABA-A receptor possibly as an antagonist (Yuan & Williams 2012). Further clinical studies need to be carried out to assess its suitability as a benzodiazepine "antidote" however it is likely that they will be difficult to carry out due the high concomitant use of opioids and benzodiazepines, but its use would not be precluded in NPS benzodiazepine overdoses. Overall the treatment of NPS benzodiazepine overdose is likely to be supportive until the drug has been excreted and will not involve the use of antidotes for benzodiazepines.

Conclusions

NPS benzodiazepines are a continuing and growing threat to public health and due to their illicit nature more NPS benzodiazepines are likely to appear on the market. NPS benzodiazepines have been shown in general shown to be more potent that the licenced benzodiazepines with longer effects. Clinicians should be aware that in overdose situation the symptoms are expected to be more severe than licenced benzodiazepines but it is likely that patients admitted for suspected NPS benzodiazepine overdose are likely to have taken other drugs as well most likely opioids. Treatment should follow the current recommended guidance for poisonings.

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Table 1: NPS Benzodiazepines reported to the EMCDDA to date

Compound	Year reported to the EMCDDA
Norfludiazepam (N-Desalkylflurazepam)	2017
Methyl clonazepam	2017
Difludiazepam (Ro 07-4065)	2017
3-hydroxyphenazepam	2016
4-chlorodiazepam (Ro5-4864)	2016
Bromazolam	2016
Desalkylflurazepam	2016
Desmethylflunitrazepam (fonazepam)	2016
Flunitrazolam	2016
Adinazolam	2015
Cloniprazepam	2015
Flutazolam	2015
Metizolam	2015
Nitrazolam	2015
Clonazolam	2014
Deschloroetizolam	2014
Flubromazolam	2014
Meclonazepam	2014
Nifoxipam	2014
Diclazepam	2013
Flubromazepam	2013
Pyrazolam	2012
Etizolam	2011
Nimetazepam	2007
Phenazepam	2007

Table 2: Pharmacokinetic Properties and "Potencies" of NPS Benzodiazepines

Benzodiazepine	Typical "dose" (mg)	Half-Life ($t_{½}$, h)	Volume of Distribution	"Potency" Based on Typical "Dose"
3-hydroxyphenazepam	1-2	?	?	+++
4-chlorodiazepam (Ro5-4864)	?	?	?	?
Adinazolam	15-30	1 – 3	2.2 l/kg	+
Bromazolam	1 -3	?	?	+++
Clonazolam	0.2 -0.4	?	?	+++++
Cloniprazepam	1 - 2	?	?	+++
Desalkylflurazepam (norflurazepam)	5-10	?	?	++
Deschloroetizolam	4-6	?	?	++/+++
Desmethylflunitrazepam (fonazepam)	1-2	?	?	+++
Diclazepam	2-3	42	?	+++
Difludiazepam (Ro 07-4065)		?	?	?
Etizolam	1-2	3.4 -7.1	0.91 l/kg	+++
Flubromazepam	4-8	106.4	?	++
Flubromazolam	0.2-0.4	10 - 20	?	+++++
Flunitrazolam	0.08-0.15	?	?	+++++
Flutazolam	5-10	3.3	690 l	++
Meclonazepam	3-6	80	100 l	+++
Metizolam	2-4	?	?	+++
Nifoxipam	0.5-1	?	?	++++
Nimetazepam	5-10	12 – 21		++
Nitrazolam	1-2	?	?	+++
Norfludiazepam (N-Desalkylflurazepam)		46 - 121	?	?
Phenazepam	1-2	6 - 80	4.7 -6.0	+++
Pyrazolam	2-3	17		+++

Dose data from http://drugs.tripsit.me/ (accessed 25th Feb 2018) other data from (Manchester et al. 2017; Huppertz et al. 2018; Barzaghi et al. 1989)**.**

Table 3: Suggested potency scale for NPS Benzodiazepines

Potency	Typical Dose (mg)
+++++	**<0.5**
++++	**0.5 – 0.9**
+++	**1.0 – 5.0**
++	**5.1 – 10.0**
+	**>10**

Table 4: NPS benzodiazepines that have been shown to give positive results for benzodiazepines in immunoassay panels.

	Detection on Benzodiazepine panel				
NPS Benzodiazepine	CEDIA	HEIA	EMIT II Plus	KIMS II	Immunalysis® Benzodiazepine ELISA
3-hydroxyphenazepam	YES	YES	YES	YES	
4-chlorodiazepam (Ro5-4864)					
Adinazolam			YES		
Bromazolam					
Clonazolam	YES	YES	YES	YES	
Cloniprazepam					
Desalkylflurazepam					
Deschloroetizolam	YES	YES	YES	YES	
Desmethylflunitrazepam (fonazepam)					
Diclazepam					YES
Difludiazepam (Ro 07-4065)					
Etizolam	YES	Partial	Partial	YES	YES
Flubromazepam	YES	YES	NO	YES	YES
Flubromazolam	YES	YES	YES	YES	
Flunitrazolam					
Flutazolam	NO	NO	NO	Partial	
Meclonazepam	Partial	NO	Partial	Partial	
Methylclonazepam					
Metizolam					
Nifoxipam	YES	YES	NO	YES	
Nimetazepam					
Nitrazolam					
Norfludiazepam (N-Desalkylflurazepam)					
Phenazepam	YES	YES	YES	YES	YES
Pyrazolam	YES	YES	partial	YES	YES

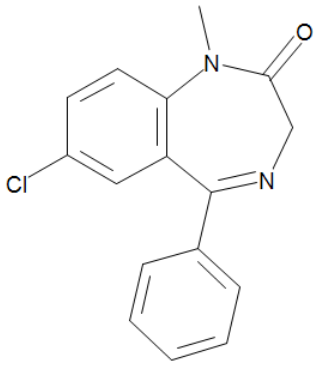
Information taken from references (Fraser et al. 1993; Lukasik-Glebocka et al. 2016; Pettersson Bergstrand et al. 2017; O'Connor et al. 2016)

Table 5: Toxidrome of Sedative-Hypnotic and Opioid Poisonings

Toxidrome	Mental Status	Pupils	Vital Signs	Other Manifestations
Sedative-Hypnotic	CNS depression, stupor, Coma	Variable	Often normal but may develop hypothermia, bradycardia, apnoea and bradypnea	hyporeflexia
Opioid	CNS Depression, Coma	Pin point	Decreased respiration, may develop hypothermia, bradycardia and hypotention	Hyporeflexia, pulmonary oedema, needle marks

Figure 1: Structure of example 1,4- and triazolo benzodiazepines

A) Diazepam



B) Bromazolam