NHS Health Scotland

Investigating the role of benzodiazepines in drug-related mortality

A systematic review undertaken on behalf of The Scottish National Forum on Drug-Related Deaths

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Executive summary

Key findings

This paper presents new developments in relation to the use and misuse of benzodiazepines and highlights significant gaps in knowledge. In particular:

- The increasing availability of unregulated benzodiazepines of unknown content and quality.
- The use of excessive benzodiazepine-type drug doses by people self-medicating with prescribed and/or illicit benzodiazepine-type drugs.
- The unclear role of benzodiazepine-type drugs in drug-related deaths (DRDs) and drug-associated mortality.
- The real risks of short-term and long-term mental health and cognitive problems associated with routine and excessive benzodiazepine-type drug use.

Background

Benzodiazepine drugs are effective medicines when used appropriately for management and treatment of various conditions from anxiety to palliative care, as well as structured alcohol and substance withdrawal. However, they also have significant abuse and misuse potential, which increases the probability of related harms, including death.

DRD is a major public health problem globally, with rates in Scotland higher than any other UK region and among the highest in Europe. Annual analysis of the National Drug-Related Death Database since 2009 has consistently shown opioids to be the most prominent group of substances involved in DRDs in Scotland. However, the vast majority of DRD cases also had a benzodiazepine present in post-mortem toxicology. Despite benzodiazepines continually featuring as a distinct component of the illicit drug market in Scotland and contributing to DRDs, there is little research on the role of benzodiazepines and benzodiazepine-type drugs in DRDs. Therefore, this has been identified as one of the priority areas for further investigation by the Scottish National Forum on Drug-Related Deaths.

Aim

To investigate why benzodiazepine-type drugs are common in drug-related mortality, and what role they play in such deaths.

Methods

A systematic integrative literature review was undertaken. The literature search utilised Embase, Medline, Cochrane Systematic Reviews and University of York Centre for Reviews and Disseminations databases. As benzodiazepines dominated the anxiolytic and hypnotic market by 1970 it was considered an appropriate start date for the literature search. Therefore, databases were searched from 1970 to March 2015.

As this study was examining the role of benzodiazepines in drug-related mortality, a reductionist approach to literature review was deliberately and intentionally avoided. Study inclusion criteria were therefore kept broad, covering major themes: benzodiazepine supply issues; pharmacokinetic and pharmacodynamic effects and interactions; adverse drug effects; polydrug use and interactions; toxicology; comorbidity; mortality; fatality and non-fatality information; and acute pharmacological overdose treatment.

The non-benzodiazepines z-hypnotics were also included in the scope of this literature review, as they are known to be misused, share a similar mechanism of action and produce benzodiazepine-like effects.

Also as part of this study, Senior Addictions Services Clinicians, Police Scotland National Drug Co-ordination Team, Forensic Toxicologists, Forensic Pathologists and Scottish Ambulance Service paramedics were interviewed as part of a wider scoping exercise.

Results

Supply and demand

The widespread use and availability of benzodiazepine-type drugs from licit and illicit sources has made it harder to legislate for and restrict access. This is partially explained by internet availability, illicit manufacture and numerous benzodiazepine-type drugs being licensed in other countries (more than 30 benzodiazepine-type drugs are available but only 16 are legislated for in the UK Misuse of Drug Regulations).

The potential for diverting licit prescription supplies to the illicit market has reduced over the last 20 years as general practice and other prescribers have steadily reduced and restricted benzodiazepine-type drug prescribing. However, the increased availability of ‘street benzos’ and the emergence of benzodiazepine-type ‘New’ or ‘Novel’ Psychoactive Substances (NPSs) have increased the complexity of substance use and related harms: self-medicating unwitting use of more potent

drugs; variability in drug potency and concentration; and easier access to larger quantities of supply.

Although it is known that illicit supplies are associated with DRDs, there is a lack of studies assessing prescribed benzodiazepine-type drug use and ‘benzo-burden’ (the total benzodiazepine-type drug load prescribed per day expressed as diazepam equivalents) in relation to DRDs, and longitudinal studies of licit and illicit drugs present in DRDs.

Pharmacokinetic considerations

Benzodiazepine-type drugs share common metabolic pathways with opioids and other drugs commonly found in DRDs. When benzodiazepine-type drugs are used at normal licensed doses in conjunction with opioids such as methadone, studies fail to demonstrate significant changes in opioid concentrations. However, substance users routinely use supratherapeutic doses or ‘megadoses’ of benzodiazepine-type drugs which are 5–10 times the licensed doses, thus increasing their risks of significant interactions, in turn increasing opioid and other drug blood concentrations, and the risk of adverse effects.

There are a lack of studies assessing drug metabolism and drug handling with high (unlicensed) doses of drugs of misuse and in overdose situations.

Pharmacodynamic considerations

Benzodiazepine-type drugs’ effects may be enhanced or diminished in the presence of other drugs, such as greater central nervous system depressive effects with alcohol or opioids. Buprenorphine is a partial opioid agonist with a ‘ceiling effect’ for respiratory depression which other opioids lack. However, this protective ceiling effect is diminished when buprenorphine is used in combination with benzodiazepines.

Central nervous system depression also occurs from the synergistic effects of other drugs commonly found with prescribed and polydrug use: antidepressants, antiepileptics, antipsychotics, other opioids, etc.

There is a lack of local and national studies assessing the differences between fatal and non-fatal ‘near-miss’ overdoses. It also may be appropriate to review and consider the role of buprenorphine in specific opioid substitution groups.

Adverse effects

Many of the benzodiazepine-type drugs’ adverse effects are commonly known: sedation, dependence, cognitive impairment, amnesia, etc. Cognitive impairment, however, may increase risk-taking behaviour and can reduce the effectiveness of psychosocial interventions and possibly even harm-reduction advice, which may play a role in DRDs. Less well known paradoxical and proarrhythmic effects may also play a significant role in DRDs.

Paradoxical effects, also known as disinhibitory effects, such as increased anxiety, inappropriate behaviour, impulsiveness and aggression, are considered to be

uncommon. However between 1% and 20% of those prescribed normal doses of benzodiazepine-type drugs can be affected, with higher doses, the use of short-acting drugs and/or co-morbid mental health problems being associated with such adverse effects.

At normal doses diazepam and other benzodiazepines have been shown to have arrhythmic effects on the heart, causing abnormal heart rhythms in susceptible individuals. These cardiac adverse effects are rarely reported with z-hypnotics. As substance users are more likely to use megadoses 5–10 times greater than a normal dose, these arrhythmic effects may contribute to DRDs. In addition, other drugs found in DRDs can cause or contribute to arrhythmias through QTc prolongation (e.g. methadone, tricyclic antidepressants) as well as comorbidities such as cardiovascular disease and electrolyte imbalance associated with liver disease.

There is a lack of studies assessing the role of benzodiazepine-type drug effects in DRDs. Future work should consider: substance-users-reported differences in disinhibitory effects between drugs; how these adverse effects effect risk-taking behaviour; the differences in benzo-burden between suicide and non-suicide DRDs; differences in QTc interval for substance users prescribed and not prescribed benzodiazepines; potential dose-response relationships between benzodiazepines and QTc prolongation.

Polydrug use and interactions

The use of more than one psychoactive substance, known as polydrug use, is common among substance users. The use of such combinations increases the risk of drug–drug and drug–disease interactions, and further increases the risk of adverse drug effects. There is a lack of clarity around the impact of these potential and actual interactions, especially with the high doses used by substance users.

There is a lack of studies assessing differences in different DRD populations (benzodiazepine implicated, present and not present); between genders; between fatal and non-fatal polydrug hospital admissions; and between different polydrug combinations and prescribed drug combinations.

Toxicology

Toxicology routinely screen for specific licensed benzodiazepines (including active metabolites) and zolpidem when investigating potential DRDs. In Scotland, zolpidem accounts for a small proportion of prescribed z-hypnotics, whereas zopiclone (not routinely screened for) accounts for the majority and has a slightly higher illicit street value than benzodiazepines. As benzodiazepine-type Novel Psychoactive Substance (NPS) use continues to grow it will further complicate routine screening.

It is unclear what role drug blood concentrations play in DRDs, as there are significant overlaps in fatal and non-fatal intoxications. As benzodiazepine-type drugs are commonly found in combination with other drugs in DRDs, greater risks are more likely to be associated with polydrug combinations.

Although it is known that benzodiazepine-type drugs are rarely found as single agents in DRDs, there is a lack of studies assessing benzo-burden and prescribing

patterns in ‘near-miss’ cases of accidental and intentional drug poisonings admitted to hospital. Owing to the widespread use of zopiclone and increased use of phenazepam and etizolam, it may be appropriate to consider their inclusion in routine screening. Due to the volume of toxicology data transferred to Police Scotland, it may be appropriate to consider single quarterly data transfers and a single point of contact between Police Scotland and Toxicology Services.

Comorbidity

In the general population it is well known that morbidity and multimorbidity increases with age. Multimorbidity is also associated with increased use of multiple prescribed medicines (polypharmacy) which in turn increases the risk of avoidable adverse drug effects. It is suspected that substance users in and out of treatment are at higher risk of developing multimorbidity and therefore will receive multiple medicines which may further complicate drug–drug and drug–disease interactions. Parallel to an ageing cohort of people who use drugs, the average age of DRDs has been increasing year on year and passed 40 for the first time in 2013.

Conditions such as chronic obstructive pulmonary disease (COPD), liver disease and psychiatric comorbidities may exacerbate benzodiazepine-type drug effects. Substance users who are life-long smokers may be at greater risk of benzodiazepine-induced respiratory depression due to compromised respiratory function.

There is a lack of studies assessing drug–disease interactions between benzodiazepine-type drugs and COPD, cardiovascular disease, liver disease and different mental health comorbidities. It may be appropriate to consider capturing common respiratory diseases: COPD, asthma and mixed asthma-COPD using separate coding.

Mortality and prescribed benzodiazepine-type drugs

There is conflicting evidence regarding benzodiazepine-type drugs being associated with increased mortality hazards for adults. However, a recent study did highlight that benzodiazepine-type drugs were associated with a greater risk of developing pneumonia and dying from pneumonia, which may play a significant role for immune-compromised substance users and those experiencing DRD ‘near-misses’ with accidental overdoses.

There is a lack of studies assessing the sequelae of non-fatal benzodiazepine-type drug overdoses in people who may subsequently die of pneumonia.

Acute pharmacological treatment of benzodiazepine-type drug overdose

The greater use of antidotes may have a positive impact on reducing DRDs, but there are limitations to their use. Flumazenil is a short-acting benzodiazepine antagonist widely available in the UK. However, it is not licensed for use in overdose, as its use can be hazardous in mixed overdoses involving tricyclic antidepressants or

in benzodiazepine-dependent patients, and requires the correction of respiratory, cardiac and metabolic conditions before administration.

Naloxone, a short-acting opioid antagonist, has been used with mixed success to reverse benzodiazepine and z-hypnotic effects. Interestingly, the studies which demonstrated a lack of effect used benzodiazepine doses at half to less than a tenth of those seen in overdoses and may not have given enough time for patients to respond. Although there are differing theories explaining why naloxone can be effective in benzodiazepine overdoses, further research is required to confirm or refute these hypotheses. However, the majority of benzodiazepine-related DRDs are commonly associated with polydrug use, often involving opioids, which presents barriers to undertaking such research.

Conclusion

The role of benzodiazepine-type drugs in DRDs is complicated by numerous factors, including the use of supratherapeutic megadoses and the lack of information about the metabolic and physical effects of such doses; the increasing use of benzodiazepine-type NPSs; polydrug use and polypharmacy further complicating adverse drug effects; low and high drug blood concentrations being present in DRDs; and benzodiazepine-type drugs being associated with increased mortality when used at routine doses.

However, in assessing the risks posed by benzodiazepine-type drugs, one must consider the risks of the alternatives such as NPS and other substances. Therefore, a better understanding of benzodiazepine-type drug use may enable the development of appropriate strategies to reduce and minimise drug-related harms, and to replicate previous achievements associated with the withdrawal of temazepam capsules.

Introduction

Drug-related death (DRD) is a major contributor to premature mortality internationally, with rates in Scotland higher than any other UK region and among the highest in Europe.[1] In the USA an epidemic of deaths caused by prescription opioids is of national concern.[2] As part of its response, the Scottish National Forum on Drug-Related Deaths (NFDRD) established a National Drug-Related Death Database (NDRDD) in 2009. This was designed to replace a series of single research studies which had investigated those deaths attributed to methadone and later deaths in drug users from all causes.[3,4] The new database was designed to provide detailed accounts of the characteristics of the individuals involved in drug-related mortality and the circumstances surrounding their deaths, and to establish a longitudinal resource to measure and observe trends in causes of DRDs. Analysis of the database provides important evidence and intelligence for policy and practice to inform future prevention and treatment strategies.

Annual analysis of the NDRDD since 2009 has consistently shown opioid use to be the most prominent substance involved in DRDs in Scotland.[5] Despite decreasing heroin presence in DRD toxicology since 2009, opioids continued to be implicated in a high proportion of deaths, as defined by the reporting pathologist. However, the vast majority of DRD cases featured individuals who had used multiple drugs prior to death, including, in many cases, diazepam. Despite continually featuring as a distinctive component of the illicit drug market in Scotland,[a,b;6–8] there is little research on the role of benzodiazepines (of which diazepam is one) in DRDs and their influence in terms of toxicology and decision-making or risk perception. Indeed benzodiazepines were one of four key topics (alongside mental health, multimorbidity and methadone overdoses) highlighted by the NFDRD to be prioritised for research in terms of their role in drug deaths.[9]

This research will therefore address one of the priority areas identified by the NFDRD, that of benzodiazepines, and be used to inform future policy and practice in this area.

[a] Stewart I, Tough A. 'The examination of illicit blue diazepam tablets'. Abertay University and Robert Gordon University; July 2014. Unpublished report.

[b] Scottish Drugs Forum. 'National Volunteers Forum. Street benzodiazepines: Blues. Qualitative study on availability and effects of illicit blue diazepam'. 2015. Unpublished report.

Background

Benzodiazepines are among the most widely prescribed psychotropic drugs in the world. Over the last 30 years Scotland has had a strong relationship with the misuse of benzodiazepines, from temazepam, diazepam, and triazolam[c] in the mid-1980s[7,10,11] to the 'New' or 'Novel' Psychoactive Substances (NPSs) such as etizolam and phenazepam in the 2010s.[5,12] This is within an environment where benzodiazepine prescribing in primary care has steadily reduced over the last 20 years[13] (see Appendix 1). In part these reductions are due to concerns about benzodiazepine dependence and inappropriate prescribing,[14,15] and have been achieved by general practitioners and prescribing support teams working to review and reduce benzodiazepine and z-hypnotic prescribing where appropriate.[16,17] Increasingly, the illicit market supply of benzodiazepines has replaced and superseded the availability of benzodiazepines on prescription. However, the vast majority of DRDs are associated with polydrug use, with benzodiazepines continuing to play a significant role in Scotland,[5] Europe,[18,19] the USA[20–23] and Australia.[24,25]

There are more than 30 different benzodiazepine drugs which share a common mechanism of action producing a range of similar effects. These can be divided into different groups based on their chemical structure and pharmacokinetic profile.[26,27] Shorter-acting drugs such as temazepam are generally used as hypnotics at night, whereas longer-acting drugs such as diazepam are usually used as anxiolytics and are considered to be less addictive. Benzodiazepines enhance the activity of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, at $GABA_A$ receptors which also have multiple sites for barbiturates, alcohol and z-hypnotic activity.[27,28] They can be administered by a variety of routes: oral, injection, buccally, intra-nasally and rectally,[29] and demonstrate varying degrees of efficacy when used to treat anxiety, insomnia, epilepsy, muscle spasms, dystonia, management of perioperative procedures, palliation, and alcohol and substance withdrawal.[29–34] Substance users may also seek illicit benzodiazepines to reduce and self-manage anxiety, insomnia and withdrawal symptoms or to improve their coping skills.[34]

As a proportion of anxiolytic and hypnotic prescribed defined daily doses (DDDs),[d] temazepam use has dropped significantly, while zopiclone use has increased significantly, since the early 1990s (Appendix 1). In part this is due to prescribers being more aware of temazepam misuse[10] and z-hypnotics being marketed and perceived as a safer alternative, although they lack any clear therapeutic advantages over benzodiazepines.[36,37] However in September 2012 the cost of temazepam in the UK increased more than tenfold, which may have encouraged further reductions

[c] Triazolam was withdrawn from the UK market in 1991 and is currently available as a prescribable medicine in some countries, such as New Zealand.

[d] World Health Organization DDDs are defined as 'the assumed average maintenance dose per day for a drug used for its main indication in adults'. They do not necessarily reflect the recommended or prescribed daily dose but provide a standardised method to compare prescribing volumes between organisations.[35]

as, anecdotally, prescribers reviewed temazepam use and considered prescribing zopiclone as a more cost-efficient alternative.

Diazepam prescribing has increased (Appendix 1) due to a combination of factors: it is the drug of choice for benzodiazepine and/or z-hypnotic withdrawal;[29,38,39] it has a range of tablet strengths allowing for greater flexibility in prescribing and allowing lower doses to be prescribed, e.g. 1mg[e] and 2mg;[29] and it has been the most cost-effective benzodiazepine for a number of years[40] (see Table 1). In general, the total benzodiazepine-type drug prescribing has reduced since the early 1990s (Appendix 1).

[e] Small diazepam doses can be given by halving 2mg tablets or using diazepam 2mg/5ml oral solution.

Table 1 Benzodiazepine equivalent doses, pharmacokinetics and prescribing information

Drug	**Approximate equivalent dose (mg)[d]**	**Time to peak for oral administration (h)[e]**	**Half-life (h) [active metabolite (h)][f]**	**Preparation**	**Cost for 28 doses[g]**
Diazepam	10	1–1.5	20–100 [36–200]	Tablets	£1.23 to £5.35
Clonazepam[a]	0.5	1–4	20–60	Tablets	£1.56*
Lorazepam	1	2	10–20	Tablets	£2.49
Alprazolam[b]	0.5	1–2	9–20	Tablets	£2.96*
Zopiclone	15	1.5–2	4–6	Tablets	£3.20 to £6.24
Zolpidem	20	0.5–3	2–6	Tablets	£3.42 to £7.12
Nitrazepam	10	2	15–38	Tablets	£5.02
Clobazam[a]	20	0.25–4	36 [79]	Tablets	£5.98*
Oxazepam	30	1–5	4–15	Tablets	£6.48 to £9.57
Chlordiazepoxide	30	1–2	5–30 [36–200]	Capsules	£9.79
Temazepam	20	1	8–22	Tablets	£13.70 to £27.36
Zaleplon	20	1	1	Capsules	£15.04*
Loprazolam	1	4	6–12	Tablets	£18.00

Drug	Approximate equivalent dose (mg)[d]	Time to peak for oral administration (h)[e]	Half-life (h) [active metabolite (h)][f]	Preparation	Cost for 28 doses[g]
Lormetazepam	1–2	1.5	10–12	Tablets	£31.04
Chlordiazepoxide	30	As above	As above	Tablets	£41.58
Midazolam	10	1	2.2	Tablets	Discontinued UK
Phenazepam[c] (fenazepam)	1	1.5–4	15–60	n/a	
Etizolam[c]	1	1–2	6	n/a	

a. Reserved for treatment of epilepsy
b. Blacklisted non-NHS; only available on private prescription.
c. NPSs
d. Approximate oral equivalents – the drug half-lives vary significantly and individual patient response will vary, therefore caution and clinical judgement is required when switching between drugs.
e. Time to peak will vary with stomach contents, gastric motility, preparation used (liquid or tablet) and route of administration (intravenous, intramuscular, rectal etc.)[41]
f. Half-life varies with patient's age, comorbidities and/or size of drug dose: older adults slower clearance, reduced in hepatic impairment[41] and may increase in overdose situations.
g. Drug costs from the Scottish Drug Tariff Part 7 April 2015[40] and BNF 69[29] (BNF drug costs are updated annually for some drugs). Some drug preparations have a range of costs depending on which tablet preparation used, e.g. oxazepam as 3x10mg or 2x15mg for 30mg dose.
Source: drug equivalent, time to peak and half-life adapted from BNF 69;[29] Ashton Manual;[38] UK Drug Misuse and Dependence Guidelines;[33] electronic Medicines Compendium;[42] Phenazepam review.[43]

Substance users report using supratherapeutic or ‘mega dose’ oral and/or intravenous temazepam and/or diazepam to boost opiate effects; intensifying intoxication and pleasure,[44–46] with median doses ranging from 40mg to 150mg.[10,44] The withdrawal of temazepam liquid capsules in the 1990s altered benzodiazepine injecting habits, with consumers in Scotland being more likely to take oral temazepam or diazepam.[6,7] For some, however, drug-related risks increased through injecting the contents of gel-filled temazepam capsules or wider experimentation and/or multiple drug use.[6] In Australia, by contrast, some changed to injecting Unisom (an antihistamine diphenhydramine) liquid capsules.[45] The withdrawal of temazepam gel capsules was associated with a reduction in benzodiazepine-associated DRDs in the UK.[47]

It is hard to estimate the prevalence of benzodiazepine use and misuse among people in opiate substitution treatment. Across Europe, 11% of those entering treatment report benzodiazepine use as a secondary drug problem, with some countries having higher reported use on entering treatment – 30% to 50%.[48] However, it should be noted that secondary drugs, including benzodiazepines, are often under-reported.[48] An audit of co-prescribing in the NHS Greater Glasgow and Clyde Health Board area in 2013 indicated that approximately 25% of people receiving treatment for opiate dependence also received one or more prescriptions[f] for benzodiazepine-type drugs in a 3-month period.[49]

As with benzodiazepines, there have also been reports of z-hypnotic misuse and dependence, with some users experiencing euphoria.[50–54] Zopiclone and zolpidem users have reported taking average daily doses of 105mg (range 60mg to 380mg) and 298mg (range 10mg to 1120mg), respectively, with the occasional case reports of injecting or snorting z-hypnotics.[51,53–55]

[f] Some of these will be single prescriptions for short-term use: benzodiazepine for alcohol withdrawal, anxiety and/or insomnia treatment. Other longer-term prescriptions may be for managed benzodiazepine reductions in line with current guidance.[29]

Methods

An extensive systematic integrative literature review was undertaken using the Embase, Medline, Cochrane Systematic Reviews and University of York Centre for Reviews and Disseminations databases. As chlordiazepoxide and diazepam were the most commonly prescribed anxiolytics and nitrazepam's share of the hypnotic market had grown significantly by 1968, 1970 was considered an appropriate start date for the literature search.[56] Therefore, databases were searched from 1970 to March 2015.

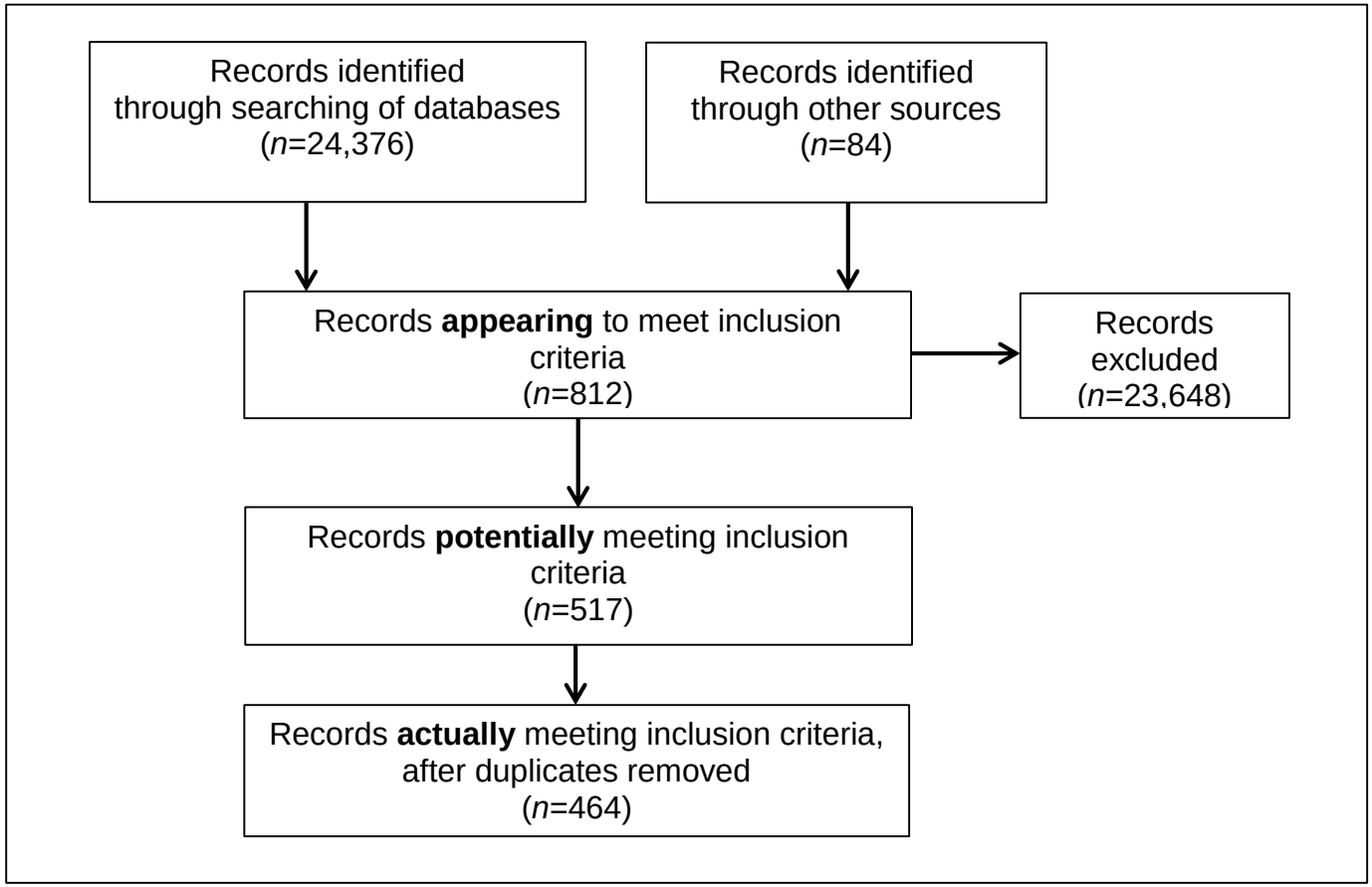
Search terms included: known benzodiazepines,[26,29,38] benzodiazepines, anxiolytics, hypnotics, mortality, death, drug-related mortality poisoning, overdose, etc. Studies were limited to English-language publications involving humans. As benzodiazepines are used to treat numerous conditions, exclusion criteria included: child, newborn, infant, sclerosis, seizures, epilepsy, alcohol withdrawal, palliative care, artificial ventilation, anaesthetic and perioperative use. Antipsychotics, barbiturates, gabapentin and pregabalin which can be used to reduce agitation and anxiety were also excluded.[29] These terms were systematically used in combination to conduct the searches (see Appendix 2 for search terms and exclusion terms used). Grey literature was identified from discussion with specialists, and reference lists, bibliographies, guidelines and internet resources were also searched where appropriate.

As this study was examining the role of benzodiazepines in drug-related mortality, a reductionist approach to literature review was deliberately and intentionally avoided. Therefore, study inclusion criteria were kept broad, covering major themes: benzodiazepine supply issues; pharmacokinetic and pharmacodynamic effects and interactions; adverse drug effects; polydrug use and interactions; toxicology; comorbidity; mortality; fatality and non-fatality information; and acute pharmacological overdose treatment.

The non-benzodiazepines, z-hypnotics, were also included in this extensive systematic integrative literature review, as they are known to be misused, share a similar mechanism of action to benzodiazepines and produce benzodiazepine-like effects.[10,50]

As part of this study, a scoping exercise was also undertaken in which healthcare and non-healthcare workers involved in treating and managing drug-related issues were interviewed. These included Senior Addictions Services clinicians, the Police Scotland National Drug Co-ordination Team, forensic toxicologists, forensic pathologists and Scottish Ambulance Service paramedics.

Figure 1 Search results



Results

Supply and demand

The widespread use and availability of different benzodiazepine drugs across the world has enabled and influences the licit and illicit sources of benzodiazepines, although recent evidence suggests that illegal 'street benzo' manufacturing is actively supplying the market with imitation benzodiazepine-type products of varying strengths and potency.[9] In Scotland in 2013/14 there were 2.1 million anxiolytic and hypnotic prescriptions dispensed to 7% (367,597) of the Scottish population, who received one or more prescriptions; 70% of these were for benzodiazepines and 28% for z-hypnotics.[13] The majority of benzodiazepine-type drugs are prescribed by general practitioners as the initiating prescriber or on the advice of specialist services such as general medicine, psychiatry, and addiction and alcohol services, where approximately 25% of those prescribed opiate substitution therapy were also prescribed a benzodiazepine and/or z-hypnotic for conditions previously outlined.[49] Anecdotally and historically, small quantities of benzodiazepines, z-hypnotics and methadone have been diverted by patients.[51,57–59] However, the wider use of instalment dispensing and supervised consumption, attempts to better control and minimise the risk of diversion, as well as more general practices reviewing and reducing prescribing in recent years have impacted on diversion, with service users themselves now acknowledging the impact of such interventions: 'So people buy as much as they have money for'.[10,16,17,33] In addition, the electronic transfer of prescriptions in Scotland has reduced the risk of them being forged or amended by people.[g]

The emergence of NPSs has increased the complexity of substance use and related harm. Benzodiazepine-type NPSs are a complex mix of licit and illicit substances for which variations in legislation and licensing between different countries affect the legality of supply within the UK.[61] Internet and 'street' sources are associated with a wide variety of benzodiazepines being available. Recent analysis of illicit 'blue' diazepam[h] demonstrates that there are wide variations in their diazepam content from zero to 48mg, with some tablets containing benzodiazepine-type NPSs such as phenazepam or etizolam[i] which are significantly more potent (see Table 1).[9]

[g] Since 2008, prescriptions issued and printed in primary care have an electronic copy, stored as a secure electronic message, and a paper copy with a unique identifier bar code. When the paper copy of the prescription is presented to the pharmacy it is scanned; the electronic version is checked and can prepopulate the dispensing information. As the prescriptions are not handwritten it reduces the potential for forged prescriptions.[60]

[h] Diazepam tablets made to resemble legitimate diazepam 10mg tablets which are blue. The analysis was carried out as partnership working between Abertay University, The Robert Gordon University and the Specialist Crime Division of Police Scotland.

[i] Phenazepam is a benzodiazepine developed in the Soviet Union in the 1970s and widely available in the Russian Federation.[43,62] Etizolam is a benzodiazepine developed in Japan in the 1970s[63] and available in Japan, India and Italy.[61]

Substance users report 'blues' and 'yellows'[j] supplies coming as loose tablets, strip packs and boxes like genuine tablets from legitimate pharmaceutical production lines with discount purchasing incentives, e.g. £1 per tablet or 28 tablets for £20–£25. Interestingly, however, zimmo's (branded zopiclone) has a slightly higher street value at £1–£2 per tablet.[10,61]

Indications from both seizure data and anecdotal feedback from peer networks suggest that drug users are taking phenazepam unknowingly and are therefore unaware of the level of risk.[62] Users also report that these drugs have varying effects from none or little effect to unexpectedly being sedated and 'being out of it for a couple of days'.[10] Historically, there have also been anecdotal reports of blue warfarin 3mg tablets being sold as 'blue' diazepam. However, benzodiazepines may also be accidentally consumed as adulterants in other illicit products such as heroin mixed with alprazolam; one of the more potent and reportedly more toxic benzodiazepines.[64–66]

Over the years there have been changes in drugs used, with a fall in temazepam and a subsequent rise and fall in diazepam use, a rise in z-hypnotic use and the recent emergence of benzodiazepine-type NPSs such as phenazepam and etizolam.[5,12,51,67] As already acknowledged, some of this change may have been driven by the withdrawal of temazepam capsules and changes in drug use,[6,7,36,45] as well as general reductions in availability as general practices restrict prescribing.[16,17] However, in assessing the risks posed by benzodiazepine-type drugs, one must consider the risk of alternatives. When New York State altered its benzodiazepine prescribing regulations in 1989, benzodiazepine-related overdoses in New York City significantly declined, whereas overdoses of other sedative-hypnotics significantly increased, with the legislation achieving no overall change in the number of sedative overdoses.[68] In the current internet age it is plausible to assume that easier access via internet supplies and NPS benzodiazepines would maintain availability, possibly even leading to increased use.[10] Although New York City has seen changes in drugs implicated in deaths, it is unclear what impact general practice benzodiazepine prescribing restrictions have had on use and misuse across the UK.

As already acknowledged, self-medicating with benzodiazepine-type drugs is common to treat withdrawal symptoms. However, it is unclear what impact current reductions in methadone prescribing[69,70] are having on benzodiazepine-type drug use, especially as average methadone doses in England and Wales are estimated to be 46mg per day[70] which is significantly lower than the 60mg to 120mg per day maintenance doses advised in current guidance.[33]

All NHS patients in Scotland have a Community Health Index (CHI) number that acts as a unique identifier and provides information on gender and date of birth.[71] The national Prescribing Information System (PIS) contains information on all NHS prescriptions dispensed in the community, of which over 95% include the patient's CHI number.[72] It is therefore possible to link PIS benzodiazepine and z-hypnotic prescribing data with individual patient records in the NDRDD, so future analysis should consider analysing prescribing patterns within the NDRDD cohort.

[j] 'Yellows' 5mg diazepam tablets.

Policy consideration

The majority of benzodiazepines and z-hypnotics which are currently licensed in the UK are 'controlled drugs' under the Misuse of Drugs Act 1971. They are listed in Schedule 4 (Part 1), except for midazolam and temazepam which are in Schedule 3 and subject to special prescription requirements and safe custody requirements.[29]

Addition of all known benzodiazepine-type NPSs to Schedule 4 (Part 1) may appear to be a solution to control drug supplies. However, this may in fact increase risks to substance users as 'street' and internet suppliers may promote and sell other drugs which have greater risks and cause more harm.

Clinical practice research considerations

- General practices are reducing benzodiazepine and z-hypnotic prescribing. What impact has reduced prescribing had on drug availability and use of alternative benzodiazepine-type drugs?
- Analysis and use of routine data from the NDRDD, PIS and other datasets to inform practice and trends by answering the following:
    - What is the prescribed benzo-burden[k] and prescribing patterns prior to DRD?
    - How does DRD cases benzo-burden and prescribing patterns compare with 'near miss' cases of intentional and accidental drug poisonings admitted to hospital?
- The proportion of people with DRDs and prescribed diazepam appears to be increasing year on year: 13% (2010), 16% (2011), 17% (2012), 21% (2013).[5] Is there an underlying trend or change in prescribed benzo-burden over the years, i.e. people prescribed lower benzodiazepine-type drug doses and/or lower doses of opiate substitute?

[k] Benzo-burden: the total benzodiazepine-type drug load, including all benzodiazepine and z-hypnotics prescribed per day, expressed as diazepam equivalents.

Toxicology and pathology research consideration

- Analysis and use of routine data from the NDRDD, PIS and other datasets to inform practice and trends by answering the following: Does the prescribed benzo-burden and benzodiazepine-type drugs found in DRD cases correlate with toxicology findings?

Pharmacokinetic considerations

Benzodiazepines are extensively metabolised in the liver by phase I and phase II metabolic processes. Phase I involves cytochrome P450 enzymes, predominantly CYP 3A4, with benzodiazepines competing for the same metabolic pathway as other psychoactive drugs, such as buprenorphine, methadone, z-hypnotics, antidepressants and antipsychotics, at normal doses, along with chronic consumption and alcohol[l] (Table 2).[39,43,73] Although buprenorphine is a CYP 3A4 substrate, there is a currently a lack of evidence supporting a pharmacokinetic interaction with benzodiazepines at normal doses.[46,74–76] Studies using routine benzodiazepine (≤40mg diazepam equivalent) and methadone doses (mean dose 50mg to 69mg) failed to demonstrate an increase in methadone concentrations, but did demonstrate greater intoxication, pupil constriction, euphoria and performance impairment.[46]

However, when substance users take supratherapeutic or megadoses of benzodiazepines, such as diazepam, which are often 3–5 times the maximum licensed dose,[10] or when these are taken as a deliberate overdose, there will potentially be greater competition for the CYP 3A4 pathway. This will reduce clearance and increase the risk of drug accumulation of one or more drugs (Table 2), potentially increasing toxicity and resulting in further problems, such as increasing blood methadone concentration.[39,75] As z-hypnotics share this same CYP 3A4 pathway and are known to be taken at 6–10 times normal dose, this will also increase the risk of interactions.[51,53] Gender also plays a role in zolpidem clearance, as females achieve up to 50% higher blood concentrations than males, putting them at greater risk of overdose.[77] In contrast, zolpidem clearance in males is reduced with lower blood testosterone concentrations.[78]

Phase II involves glucuronidation with benzodiazepines being predominantly metabolised by uridine diphosphate glucuronosyltransferase (UGT) 2B7 enzyme. Unlike other benzodiazepines which undergo extensive metabolism in phase I, lorazepam, oxazepam and temazepam are substrates for UGT 2B7 and are predominantly metabolised by glucuronidation prior to excretion (see Table 2). However, the metabolism of these drugs is complicated by the fact that some benzodiazepines, such as diazepam, inhibit glucuronidation. In phase I metabolism at normal therapeutic doses, diazepam is transformed to its active metabolites,

[l] Ethanol is predominantly metabolised by alcohol dehydrogenase. In alcohol misusers CYP 2E1 plays a significant role in metabolising ethanol to acetaldehyde, which is then metabolised by aldehyde dehydrogenase. Chronic alcohol consumption induces CYP 3A4, CYP 1A2 and CYP 2B6.[40]

oxazepam and temazepam, which are UGT 2B7 substrates. However, the parent drug diazepam can inhibit UGT 2B7 activity, which will result in active metabolite (oxazepam and temazepam) accumulation and increased drug effects, especially when megadoses are taken by substance users or in overdose.[79] As morphine is also a UGT 2B7 substrate, diazepam will inhibit its metabolism and diazepam's active metabolites (oxazepam and temazepam) will compete with morphine for UGT 2B7 glucuronidation, increasing the blood concentrations of one or more of these drugs.

It would be expected that the use of megadoses by substance users will increase the potential for adverse drug effects due to higher blood concentrations. However, evidence is lacking for a clear linear relationship between benzodiazepine blood concentrations and DRD, as low to very high benzodiazepine concentrations have been implicated in DRDs.[43,80,81] As with other drugs, it is suspected that there will be significant variations in benzodiazepine-type drug tolerance and susceptibility between individuals due to: variations in previous drug use; drug handling and clearance, possibly affected by phase I and II metabolism such as enzyme saturation; inhibition and/or competition due to benzodiazepine-type drugs and their metabolites; comorbidities and drug–drug interactions with prescribed drugs and polydrug use.[82]

Toxicology and practice research consideration

- Does the metabolism of benzodiazepine-type drugs change when very high doses (unlicensed doses) are used and does this affect the metabolism of other drugs commonly found in DRDs?

Table 2 Interactions of psychotropic drugs with cytochrome P450 and glucuronidation

Enzyme systems	**Benzodiazepines and z-hypnotics**	**Opioids**	**Tricyclic antidepressants**	**SSRIs**	**Other ADMs**	**Alcohol**	**Antipsychotics**
CYP 2C19	Diazepam (S) ++ Nordiazepam (S) ++	?Methadone (S)+	Imipramine (S) + Trimipramine (S) +	Citalopram (S) ++ Escitalopram (S) +++ Escitalopram (I) + Fluoxetine (S) + Sertraline (S) +			
CYP 3A4	Alprazolam (S) +++ Clonazepam (S) +++ Diazepam (S) ++ Etizolam (S) +++ ?Flurazepam (S) +++ Midazolam (S) +++ Nitrazepam (S) +++	Buprenorphine (S) ++ Methadone (S) +++	Amitrptyline (S) ++ Clomipramine (S) ++ Dosulepin (S) +++ Trimipramine (S) +	Citalopram (S) ++ Fluoxetine (S) + Fluoxetine (I) +++ Fluvoxamine (I) ++ Paroxetine (I) +++ Sertraline (S) +	Trazodone (S) +++ Venlafaxine (S) ++	Intoxicated (S) ++	Aripiprazole (S) +++ Chlorproimazine (S) ++ Clozapine (S) + Quetiapine (S) +++ Risperidone (S) + Sertindole (S) +++

Enzyme systems	Benzodiazepines and z-hypnotics	Opioids	Tricyclic antidepressants	SSRIs	Other ADMs	Alcohol	Antipsychotics
	?Phenazepam (S) Triazolam (S) +++ Zaleplon (S) +++ Zolpidem (S) +++ Zopiclone (S) +++						
Glucu UGT 2B7	Clonazepam (I) Diazepam (I) Flunitrazepam (I) Lorazepam (S & I) Nitrazepam (I) Oxazepam (S & I) Temazepam (S)	Buprenorphine (S) Morphine (S)	Amitriptyline (I) Clomipramine (I)				Chlorpromazine (I)

ADMs: antidepressant medicines; CYP: cytochrome P450; Glucu: glucuronidation; I: inhibitor. S: substrate; SSRIs: selective serotonin re-uptake inhibitors.

+ low (clinically insignificant at normal doses); ++ medium (clinical significance unclear/unknown at normal doses); +++ high (clinically significant at normal doses); ?: probably metabolised by enzyme.

Amended from Maudsley, phenazepam, etizolam and glucuronidation studies.[39,43,73,79]

Pharmacodynamic consideration

As outlined above, changes in drug handling due to dose taken, reduced clearance, accumulation, etc., will affect drug pharmacodynamics – the action of drugs on the physiology or pathology of the body. The concomitant use of another drug or multiple drugs may enhance or diminish pharmacodynamic effects, for example alcohol enhancing the central nervous system (CNS), depressive effects of benzodiazepines and vice versa or increasing paradoxical effects.[83] However, as well as being a central nervous system depressant, alcohol acts at the $GABA_A$ receptor complex and can affect benzodiazepine metabolism as outlined above.

Buprenorphine is a partial opioid agonist with a 'ceiling effect' for respiratory depression, which potentially offers safety advantages over other opioids, and is commonly used in some countries as an opiate substitute.[74] Interestingly, although pharmacokinetic interactions between benzodiazepine-type drugs and buprenorphine are currently thought not to occur when normal doses are used, there are additive and/or synergistic interactions increasing CNS depressive effects, reducing and inhibiting the protective respiratory depression 'ceiling effect'.[46,74–76] However, as noted above, substance user benzodiazepine megadoses are commonly 5 to 6 times higher than the maximum licensed doses, with the use of such doses significantly increasing the potential for greater CNS depression. The potential use of megadoses is of concern as DRDs have occurred when buprenorphine and benzodiazepine drug concentrations have been within the normal therapeutic range.[84–87]

Studies which indicate that buprenorphine is safer than methadone rarely consider or report combination benzodiazepine use or the differences between cohorts prescribed methadone or buprenorphine.[70,88,89] One study did consider benzodiazepine prescription use, although it did not consider benzo-burden or total daily dose used. It reported greater accident and emergency use and a greater risk to females who were co-prescribed buprenorphine and benzodiazepines over a 12-month period.[90] Unfortunately, the study sample was too small to assess for overdose death rates, substance users who were considered to have an atypical response to benzodiazepines were excluded and users attended an intensive outpatient programme. All of which may have excluded more chaotic individuals with greater drug-related risks/behaviours that may increase their risk of DRD. Another study acknowledged that the difference between unsupervised methadone (up to four doses dispensed weekly, unsupervised) and supervised buprenorphine (rarely prescribed unsupervised) consumption may have had a role in contributing to less drug diversion, although they did not think this influenced the overall benefits seen with buprenorphine.[88]

At first glance the French experience with buprenorphine appears compelling, with an 80% reduction in DRDs between 1995 and 1999, after the loosening of restrictions on buprenorphine prescribing in 1996.[91] The changes in legislation allowed all registered medical doctors to prescribe buprenorphine without a requirement for supplementary educational programmes or special licensing, and community pharmacies to dispense buprenorphine, resulting in the wider use of opiate substitution treatment within general practice, with buprenorphine accounting

for 80% of that treatment. At the same time buprenorphine legislation changed in France, needle exchange programmes were introduced and there was a possible change in attitude towards intravenous drug users by health care providers.[91] In contrast, methadone prescribing remains restricted to doctors working in state-licensed substance abuse clinics or hospitals where prescriptions are initially dispensed only on site.[91] The observed differences in DRD rates between patients treated with buprenorphine and methadone[89] may be due to subtle differences between these populations, general practice and specialist care, which may be associated with variations in lifestyle and risk-taking behaviours. Those under specialist care receiving methadone may have more chaotic lives, greater risk-taking behaviours and/or greater polydrug use.

Despite the apparent success of the French buprenorphine policy, it is concerning that 45% of people in opiate substitution treatment in France currently use benzodiazepines,[48] which would be expected to increase the risk of DRD. Moreover, there are still multiple confounding factors which may have played a role in the observed DRD reductions in France. Indeed DRDs are still occurring to a lesser extent, and with buprenorphine there is still the issue that the majority of these deaths are due to polydrug use.[46,74–76,84,88] One further concern with increased buprenorphine use is its poor response to naloxone,[74] therefore wider use may work against potential DRD reductions achieved through Scotland's national naloxone programme.

Other synergistic CNS depressant effects such as cognitive impairment, increased sedation, respiratory depression, etc., also occur when benzodiazepine-type drugs are used in combination with other opioids, tricyclic antidepressants (TCAs), antiepileptics, antipsychotics, sedating antihistamines and others, and will be further complicated by polydrug use.

Clinical practice consideration

- Review of current buprenorphine use in the context of significant DRD reductions in France. Would it be appropriate to increase buprenorphine use in specific opiate substitution cohorts?

Clinical practice research considerations

- Within Scotland what are the differences between buprenorphine and methadone DRDs with/without benzodiazepines?
- How does this compare with 'near-misses' and are there cohort effects?

Policy consideration

- Review on the appropriateness of wider buprenorphine use in specific opiate substitution treatment cohorts.

Adverse effects

Many of the benzodiazepine and z-hypnotic adverse effects are commonly known: sedation, cognitive impairment, amnesia and dependence,[29] with higher doses being associated with more CNS depression[65] and cognitive impairment, as seen with road traffic accidents[92,93] and risk of falls in the elderly.[94] More recently, studies have shown an association between benzodiazepine use and dementia. However, these studies do not show causation and acknowledge that benzodiazepine use may be associated with the treatment of prodromal dementia symptoms.[95–98]

Cognitive impairment is of concern as it may affect substance users' risk of 'double dosing' or taking multiple doses due to forgetfulness. Benzodiazepines are known to affect delayed recall (information presented minutes or hours earlier) rather than immediate recall (information presented seconds earlier). Different benzodiazepines have different amnesiac effects, such as short-acting drugs (lorazepam, flunitrazepam and triazolam) affecting recall more than longer-acting drugs (clonazepam, diazepam, oxazepam, etc.), although variations in dose may also influence amnesiac effects.[68,99] These cognitive effects are associated with poorer psychotherapy outcomes in some conditions such as post-traumatic stress disorder,[100] and may influence the outcomes in other anxiety disorders.[101] However, variations in different psychotherapies, treatment engagement and adherence, and poorer motivation to changes in substance-use patterns may also contribute to poorer psychotherapy outcomes.[100] Long-term benzodiazepine use is associated with significant cognitive impairment,[102] and improvements in cognitive function are seen after benzodiazepine withdrawal. However, some individuals' cognitive impairment may continue for years after withdrawal.[27,103] Therefore, it may be more appropriate for substance users to minimise benzodiazepine use before engaging with psychosocial interventions to help optimise treatment outcomes.

Less well-known effects, such as paradoxical and proarrhythmic[m] effects, may have significant effects in drug-related risks and DRDs.

Paradoxical effects and decision making

Paradoxical, also known as disinhibitory, effects of benzodiazepines, such as increased anxiety, insomnia, agitation, paranoid ideation, excessive tearfulness, inappropriate sexual behaviour, aggression and violence, are considered to be uncommon, affecting <1% of patients prescribed doses within the normal range. However, between 1% and 20% of those prescribed benzodiazepines may be affected,[39] with higher doses, the use of short-acting drugs and/or comorbid mental

[m] An abnormality of cardiac rhythm such as a slow (bradycardia), fast (tachycardia) and/or irregular heart beat is a called a cardiac arrhythmia. Cardiac arrhythmias are caused by a defect in the generation or conduction of electrical impulses in the heart. Drugs which interfere with generation or conduction of electrical signals are commonly termed proarrhythmic. Drugs which are used to treat arrhythmias, such as digoxin, have antiarrhythmic properties; however, at high and toxic doses digoxin demonstrates proarrhythmic effects and can cause slow or fast heart rate.[26]

health problems – such as personality disorder – being associated with a higher incidence of paradoxical effects in susceptible individuals,[39,104,105] especially those with poorer impulse control.[106] In a small study (*n*=100), 55% of drug users reported disinhibitory violent and aggressive behaviour with temazepam use,[8] where median temazepam and diazepam doses range from 40mg to 150mg[10,44] as opposed to the maximum licensed daily doses of 40mg and 30mg, respectively.[29] To a lesser extent, paradoxical effects including visual hallucinations, euphoria, disinhibition and agitation have been reported with z-hypnotics, especially zolpidem, at routine and higher doses.[51,53,107–112]

Disinhibition associated with benzodiazepine-type drugs may be further intensified by benzodiazepine and/or z-hypnotic-induced cognitive impairment[29] affecting substance users' response to seek help when they observe or are experiencing an overdose. When alcohol is taken in combination with benzodiazepine-type drugs it can act synergistically, amplifying disinhibitory and dissociative behaviours.[106,107]

Benzodiazepine-type drug use is also associated with suicidal thoughts and suicide attempts. With no evidence of causality, however, it is only one of the many factors which are associated with suicide in both the general and substance-using populations.[107–109,113–115] Depression plays a more significant role, with around a quarter to a third of heroin users meeting the criteria for major depressive disorder,[59,113,115] which benzodiazepine and/or z-hypnotic use is known to aggravate.[68,110,116] Although benzodiazepine and methadone users report more deliberate overdoses than methadone-only users,[117] it is hard to clarify if benzodiazepines increase suicidal behaviours in the substance-using populations, as it may just be one of the many contributing factors associated with a drug-using lifestyle which puts susceptible individuals at greater risk.[59,115]

Clinical practice research considerations

- Do substance users report difference in disinhibition with different benzodiazepine-type drugs and what dose relationship might there be?
- Do disinhibitory effects affect user response to seek help and/or use naloxone?
- What is the difference in benzo-burden between suicide and non-suicide DRDs?
- How much of an improvement in depressive symptoms is achieved with managed withdrawal of benzodiazepine-type drugs in users stabilised on opiate substitution treatment?

Arrhythmic effects

Diazepam has been shown at normal doses – 14mg intravenous (15mg orally) – to significantly shorten cardiac sinus cycle length and improve atrioventricular node conduction without significant effects in other cardiac tissues, which may present as proarrhythmic and antiarrhythmic effects in susceptible patients.[118] At normal doses, diazepam and other benzodiazepines have been shown to reduce blood pressure and increase heart rate, which is only partially explained by reductions in blood pressure. However, autonomic neurocardiac regulation may be influenced first by reductions in central vagal tone and second by direct decreases in the cardiac pacemaker.[119] This runs contrary to an older small study (*n*=10)[41] which observed a weak correlation with blood concentrations of benzodiazepines and heart rate but did not correlate with ECG changes. However, 4 in 10 patients had also taken antipsychotics or TCAs, which are known to have arrhythmic effects.[29] There have also been reports of phenazepam causing tachycardias and bradycardias in acute poisoning,[43] but arrhythmias and cardiac toxicity are rarely reported with z-hypnotics.[28]

The observed proarrhythmic effects with normal benzodiazepine doses need to be considered in the context of DRDs, substance use and treatment. Substance users tend to take much higher megadoses of 100mg to 150mg diazepam or 100mg zopiclone.[10,51] A large proportion are also co-prescribed antipsychotics, antidepressants and/or methadone,[120] which are known to cause QTc[n] prolongation with larger doses causing greater QTc prolongation.[122,123] QTc prolongation is of concern as it is associated with ventricular tachycardia and sudden cardiac death which cannot be confirmed from autopsy findings.[121] Older users with multimorbidity, such as cardiovascular disease or electrolyte imbalances associated with liver disease, and polydrug use are at greater risk of these adverse effects.[5,124–126]

Clinical practice research considerations

- Are there differences in QTc interval for substance users prescribed regular benzodiazepines and not prescribed regular benzodiazepines?
- Is there a dose response relationship between QTc prolongation and regular low, medium, high and supratherapeutic megadose benzodiazepine use?

[n] The QT interval on an electrocardiogram describes the manifestation of ventricular depolarization and repolarisation. The QT interval is influenced by heart rate, therefore it should be measured for rate correction allowing the calculation of the corrected QT interval (QTc). Bazett's formula is considered the gold standard for QTc calculation.[121]

Polydrug use and interactions

The use of more than one psychoactive substance, known as polydrug use, is common among substance users.[127] As already acknowledged, concomitant use of benzodiazepine-type drugs with other substances may be used to reduce adverse effects of other drugs such as insomnia and/or anxiety or to enhance the effects of opioids.[44–46] Polydrug use further complicates and increases the risk of drug–drug and drug–disease interactions, increasing the risk of adverse drug effects. Polydrug use accounts for 13% of drug-related hospital admissions[128] and 97% of DRDs have multiple drugs present in the body at death, with more than one drug implicated in 68% of DRDs in Scotland.[5]

Alcohol is commonly found in combination with benzodiazepines in DRDs and interacts synergistically to increase CNS depression. There may be some variation in effects between different benzodiazepines, as diazepam and chlordiazepoxide pose a smaller risk of death by poisoning than temazepam when given as a hypnotic to patients suffering from alcoholism.[129] However, these patients may not have taken the larger doses associated with substance use which may negate the observed differences in toxicity. Among the z-hypnotics, zolpidem is more commonly reported as causing adverse effects and demonstrating greater toxicity in combination with alcohol and other drugs, although the fatal toxicity index is lower for z-hypnotics; zolpidem and zopiclone estimates of ~2 deaths per million versus ~7 for benzodiazepines and ~150 for barbiturates,[28,130,131] and adverse media attention may have influenced adverse event reporting in some countries.[107]

Methadone substitution programmes are associated with reductions in DRDs.[132,133] Historically, however, co-prescribing of benzodiazepines in such programmes was common and was found to be associated with an increased risk of DRD.[75,120] Addiction services have worked to reduce co-prescribing[134] and co-prescribing of diazepam has been low but slowly rising in the DRD cohort, up from 13% in 2010 to 21% in 2013.[5] In part this may be due to diazepam being prescribed in preference to other benzodiazepines and/or z-hypnotics; diazepam being the drug of choice for managed benzodiazepine withdrawal[29,33,34] and trends mimicking those within the general population (see Appendix 1).

The combination of benzodiazepines and methadone use versus methadone-only use has also been shown to be associated with increased QTc prolongation.[135,136] So far such adverse effects have not been reported for z-hypnotics, which are prescribed at lower doses than benzodiazepines. Peles et al[135] noted that those receiving benzodiazepines had significantly longer QTc prolongation but were also prescribed significantly higher methadone doses (129 ± 30mg/day vs. 104 ± 38mg/day). Meanwhile Mijatovic et al[136] indicated that there was a significant correlation between diazepam dose (mean dose 31±10mg) and QTc prolongation, without a similar correlation with the methadone dose (mean dose 45± 15mg). Increased QTc prolongation with combination use of benzodiazepine and methadone may also be due to a combination of effects: reduced clearance of one or both substrates through competition for CYP 3A4 resulting in increased levels, or changes in heart rate and cardiac pacing[39,118,119] which may be further exacerbated by comorbidities or metabolic imbalances.[121] Risk of sudden death, which is associated with QTc prolongation, is hard to quantify and qualify, with a recent Cochrane review

concluding it was not possible to draw any conclusions about the effectiveness of QTc screening strategies for preventing cardiac morbidity/mortality in methadone-treated substance users.[137] To further complicate QTc issues, there is a lack of expert consensus on what constitutes prolongation and when to treat.[138]

Where small to high doses of TCAs, such as amitriptyline, are added to benzodiazepine and methadone combinations it is expected that there will be further increases in cardiac toxicity risk and QTc prolongation, which are directly correlated with TCA dose.[122,139] Blood drug concentrations would possibly also increase, as all three drugs are substrates for the CYP 3A4 pathway, in turn increasing synergistic effect such as CNS depression. Such a scenario could result in further cardiac toxicity and respiratory depression, which is associated with greater mortality rates.[21,140,141]

CNS and respiratory depression is a synergistic pharmacodynamic effect associated with the use of other opioids such as heroin, morphine, oxycodone, buprenorphine and tramadol alongside benzodiazepine-type drugs. As already acknowledged above, in overdose situations competition for phase II (glucuronidation pathways) may reduce the clearance of drugs competing for the same pathway leading to higher blood concentrations and subsequently greater adverse effects.[79] However, there is also at least one case report of lorazepam antagonising the effects of morphine.[83]

Clinical practice research considerations

- What are the differences in DRD subpopulations with and without benzodiazepine-type drugs present: 20–30% not present, 40–50% present and 20–30% implicated?
- Where alcohol is present in combination with benzodiazepine-type drugs, is there an increase in proportion of female deaths due to lower capacity to metabolise alcohol than males?
- What is the role of benzodiazepine-type drugs and polydrug combinations in fatalities and non-fatalities for drug-related hospital admissions?
- Is there a dose response increase in QTc for methadone maintenance service users co-prescribed diazepam and methadone?
    - Fixed methadone dose with low (≤10mg/day), medium (>10mg≤20mg/day), high (>20mg≤30mg/day), very high (>30mg/day) diazepam dose.
    - Fixed methadone dose with low (≤10mg/day), medium (>10mg≤20mg/day), high (>20mg≤30mg/day), very high (>30mg/day) total benzo-burden as diazepam equivalents.
    - Are there gender, age and ethnicity differences between subgroups?

- Does QTc interval change for service users co-prescribed diazepam and fixed-dose methadone and diazepam managed reductions, diazepam starting dose >30mg/day.
- Are there gender, age and ethnicity differences between subgroups?
- What are the risks associated with co-prescribed drug combinations, such as methadone, TCAs and benzodiazepines?

Toxicology

When investigating potential DRD cases in Scotland, toxicology units routinely screen for: diazepam, nordiazepam (active metabolite), temazepam, oxazepam, lorazepam, chlordiazepoxide, nitrazepam and zolpidem. In Scotland, zolpidem and zopiclone account for 5% and 24%, respectively, of all benzodiazepine and z-hypnotics dispensed in primary care, with zopiclone prescribing continuing to increase as a proportion of all benzodiazepine-type drugs.[13] In part this is due to zopiclone being prescribed in preference to temazepam which has significantly increased in cost. Due to the widespread use of zopiclone and substance users acknowledging its use, it would seem appropriate to include zopiclone in routine screening.[10]

Due to z-hypnotics having a short half-life it has been suggested that in z-hypnotic-related deaths the maximum recommended time interval for detection is 48 hours in blood and 72 hours in urine.[30] However, due to the volume of DRDs and autopsies in the west of the country, some samples may be taken up to 7 days or more after death, therefore antemortem elimination may have already occurred. This will be especially problematic where zaleplon has contributed to DRDs due to its significantly shorter half-life and the very short sampling window allowing for blood analysis. Therefore, although zaleplon may potentially contribute to DRDs it will be very difficult to qualify and quantify its role.[28] As benzodiazepine-type NPS use and presence in DRDs is increasing, it may also be appropriate for phenazepam and etizolam to be included in routine testing.[5,12]

It is unclear what role blood concentrations play in the risk of benzodiazepine-related DRDs, as there are significant overlaps in fatal and non-fatal intoxications.[41,81] This is also an issue for fatal and non-fatal methadone intoxications,[142] complicating the certainty with which drugs are implicated in individual DRDs. However, polydrug use may be of more importance here, as the majority of benzodiazepine DRDs include other drugs.[20] Higher morphine and methadone concentrations are seen in morphine-only and methadone-only DRD cases when compared with the polydrug cases with the same opioid,[67,143] resulting in greater toxicity with combination use.[21,25,46,76]

Discussions with Police Scotland identified a preference for toxicology data to be reported as a single national dataset, with one central point of contact at the end of each quarter. This would help to improve continuity, minimise error, and enable dataset mismatches to be identified and dealt with at one point in time. Toxicology indicated that the data is owned by the Procurator Fiscal and permission would need

to be agreed and granted for the data to be transferred as agreed within protocol. However, toxicology should not be used outwith the context of the case, to avoid coming to incorrect conclusions about the cause of death, e.g. a fall from height or major trauma causing a death which was not necessarily associated with drug levels.

Toxicology practice and research considerations

- Zopiclone to be included in routine screening with zolpidem.
- Phenazepam and etizolam to be included in routine screening.
- How do benzodiazepine-type drug patterns present in toxicology change with time?
- Are there geographical hotspots in relation to benzodiazepine-type drugs being reported in DRDs and do these hotspots changing with time?

Police Scotland consideration

- Toxicology reporting and data transfer to be discussed with Procurator Fiscal's Office to consider and agree a single quarterly data transfers with single point of contacts between Police Scotland and Toxicology Services.

Clinical practice research consideration

- How does DRD cases benzo-burden and prescribing patterns compare with 'near miss' cases of intentional and accidental drug poisonings admitted to hospital?

Comorbidity

The UK population is ageing with the proportion of over 65 years olds in Scotland projected to increase from 18% (0.95/5.33 million) in 2013 to 25% (1.47/5.78 million) in 2037.[144] Moreover, the proportion of the population estimated to be problem drug users over 35 years old also increased from 42% in 2009/10 to 48% in 2012/13,[145] while the proportion of individuals over 40 years olds attending for an initial assessment at specialist drug treatment services increased from 15% in 2006/07 to 26% in 2012/13.[146] In addition, an English study also indicated that there was significant growth in older (50 to 74 years old) substance users and highlighted that these people were more likely have poorer health and die of non-DRD causes than DRDs when compared with younger substance users.[126]

In the general population it is well known that morbidity and multimorbidity increases with age, with multimorbidity occurring 10–15 years earlier in people living in the most deprived areas.[147] Multimorbidity is also associated with increased polypharmacy,[o] where patients are prescribed multiple drugs for multiple conditions on the advice of multiple specialists or in line with multiple clinical guidelines,[147] increasing the risk of avoidable adverse drug effects and hospital admissions.[148,149] It is suspected that substance users in and out of treatment will be at higher risk of developing earlier multimorbidity and therefore receive multiple prescription medicines for these conditions which will further complicate drug–drug interactions and drug–disease interactions. An Italian study has also shown that benzodiazepine users (benzodiazepine only vs. methadone maintenance and benzodiazepines vs. methadone only) using the 12-item General Health Questionnaire rate their health as being much worse than methadone-only patients, who rate their health as being comparable to the general population.[150]

As the majority of substance users smoke and are known to have reduced pulmonary function,[124] we would expect there to be a greater prevalence of chronic obstructive pulmonary disease (COPD) in this population than in the general population. We would also expect older users to have more severe COPD, as with the general population, as they will have smoked for longer. However, previous studies have only captured asthma information or categorised all respiratory conditions in a single category.[5,126,151] As benzodiazepine-type drug, and/or opioid, overdoses cause respiratory failure, and moderate/severe COPD can also cause respiratory failure, we would expect to see synergistic effects with both factors contributing to DRDs.[152]

Liver disease may reduce benzodiazepine and z-hypnotic clearance, increasing the drug's half-life and prolonging drug effects, with these varying with disease severity and drug used. For example, oxazepam's clearance is less affected by hepatic failure at normal doses.[41,79] It has also been reported that overweight patients' greater liver size results in a greater quantity of enzymes, providing greater metabolic capacity.[79] However, overweight patients have a greater risk of sleep apnoea, which is a known contra-indication for the use of benzodiazepines and z-hypnotics,[29] with a recent study also highlighting the association between obesity (mean body mass index 39 kg/m^2) and short-acting hypnotics.[153] Conversely, underweight and/or malnourish users may be more susceptible to adverse drug effects and DRD due to lower hepatic capacity and reduced drug protein binding.

Cardiovascular disease may also be associated with an increased risk of DRD, as some conditions – heart failure, cardiomyopathy, acute and chronic alcohol abuse – are more likely to be associated with arrhythmias.[152]

Benzodiazepines-type drugs also play a conflicting role in relation to mental health. However, benzodiazepine-type drugs can be effective for alcohol and substance withdrawal; short-term management of anxiety;[29–31,33,34] and are of marginal benefit for the short-term treatment of insomnia.[154,155] Longer-term use is associated with

[o] The term polypharmacy just means 'many medications' and has often been defined as a patient taking five or more medications.

greater depressive symptoms[68,110,116] and depression is known to be associated with greater substance user mortality.[125,156]

Practice consideration

- Future DRD and substance misuse databases should capture and code separate respiratory diseases: COPD, asthma, mixed asthma COPD and respiratory other.

Clinical practice research considerations

- Do a greater proportion of DRDs involving benzodiazepine-type drugs have COPD in comparison with benzodiazepine-type drug users who are ‘near-miss' survivors?
- Within the DRD cohort where benzodiazepine-type drugs are present, are there changes in the proportions of individuals with hepatic disease or cardiovascular disease when compared with the non-benzodiazepine-type drug cohort?
- Are there associations between body mass index and benzodiazepine-type drugs in DRDs?
- What impact does managed benzodiazepine-type reductions have on mental health such as depressive symptoms, cognition and coping skills, and substance use behaviours?

Mortality and prescribed benzodiazepine-type drugs

A recent large UK general practice population database study indicated that benzodiazepines and/or z-hypnotics drugs are associated with increased mortality hazards for adults.[157] Within this study, attempts were made to adjust for confounding factors such as age, gender and comorbidities, but unfortunately it has been widely reported that common mental health problems which benzodiazepine-type drugs can be prescribed for are poorly coded in general practice, placing some of the findings in doubt.[158–160] A recent US veterans study also indicated that there was an associated increased risk of overdose death for people co-prescribed benzodiazepines (z-hypnotics where excluded) and opioids, with the main factors being: co-prescription of benzodiazepines and opioids; longer duration of benzodiazepine prescription; and an increased risk of death with higher benzodiazepine doses prescribed.[161] Unfortunately, this study used the long-acting drug clonazepam as their drug reference when comparing the risks between different

benzodiazepines, demonstrating that other drugs were safer.[p] Compared with UK benzodiazepine prescribing there was a larger proportion of people in wealthier areas receiving benzodiazepines.[162] However, other studies present a more mixed picture, with benzodiazepine-type drugs being associated with varying mortality hazards in different populations: increased mortality hazards in middle-aged populations and substance misuse populations, but not in elderly populations.[120,163,164]

The use of benzodiazepine-type drugs has been associated with a significantly greater risk of developing pneumonia and dying from pneumonia, with some drugs having greater risks than others (Table 3).[165] Chlordiazepoxide was not associated with increased pneumonia incidence, possibly due to its short,term use for alcohol withdrawals, and lorazepam was associated with increased hazard ratio for 30-day mortality, which may reflect its greater use in care home populations.[166] The association between benzodiazepine-type drug use and pneumonia may play a significant role for immunocompromised substance users and those experiencing DRD near misses with accidental overdoses.

Clinical practice and pathology consideration

- What are the proportion of non-fatal benzodiazepine-type drug overdoses that subsequently die of pneumonia?

[p] Using alprazolam as a reference may have been more appropriate, as it demonstrates greater toxicity than other benzodiazepines in overdose.[65]

Table 3 Benzodiazepine-type drugs associated with the occurrence of pneumonia and mortality from pneumonia

Drug	**Association between exposure and pneumonia incidence**	**Association between 30-day and long-term mortality**	
	***Adjusted OR (95% CI), *p*-value**	**30-day** ***HR adjusted (CI 95%), *p*-value**	**Long-term** ***HR adjusted (CI 95%), *p*-value**
Benzodiazepine	1.54 (1.42 to 1.67), *p*<0.001	1.22 (1.06 to 1.39), *p*=0.004	1.32 (1.19 to 1.47), *p*<0.001
Diazepam	1.49 (1.34 to 1.65), *p*<0.001	1.24 (1.04 to 1.47), *p*=0.014	1.27 (1.11 to 1.46), *p*=0.001
Lorazepam	1.65 (1.24 to 2.20), *p*=0.001	1.61 (1.14 to 2.28), *p*=0.007	1.48 (1.10 to 2.00), *p*=0.010
Chlordiazepoxide	1.19 (0.88 to 1.62), *p*=0.248	1.58 (0.98 to 2.57), *p*=0.063	1.49 (1.02 to 2.17), *p*=0.038
Temazepam	1.43 (1.29 to 1.59), *p*<0.001	1.11 (0.95 to 1.29), *p*=0.208	1.20 (1.06 to 1.36), *p*=0.003
Zopiclone	1.98 (1.49 to 2.64), *p*<0.001	0.93 (0.55 to 1.53), *p*=0.738	1.11 (0.77 to 1.60), *p*<0.564

Adapted from Obiora et al.[165]
*Adjusted for age, sex, Townsend deprivation score, smoking status, Charlson comorbidity index score, alcohol use, depression and psychosis.
HR: hazards ratio; OR: odds ratio

Acute pharmacological treatment of overdose

Non-fatal overdoses are observed among a large proportion of substance users.[59,167] Among fatal overdoses in Scotland, it is also well documented that ambulances are consistently called to more than 80% of cases recorded as DRDs.[5] Among the cases where an ambulance did not attend, there were 4% when an ambulance was not required because it was clear that the deceased was beyond medical intervention.[5] The greater use of antidotes such as naloxone by substance users, associates and family may have a positive impact on reducing DRDs.[168]

Flumazenil, a short-acting benzodiazepine antagonist, is widely available in the UK but not licensed for use in overdose. This is possibly because flumazenil use in overdose can be hazardous, particularly in mixed overdoses involving tricyclic antidepressants or in benzodiazepine-dependent patients, and requires the correction of respiratory, cardiac and metabolic conditions before administration.[29,169] Flumazenil also needs to be administered intravenously, which may be impractical for emergency use as intravenous access is not always possible in some substance users. Despite this, some non-UK ambulance services have reportedly used flumazenil in a minority of patients.[170] UK ambulance service guidance does not advocate this, due to the significant risks associated with destabilising patients.[171,172] A French survey of accident and emergency flumazenil use considered it to be dangerous and/or contraindicated in 38% of patients who received it due to patients being chronic benzodiazepine users, taking benzodiazepines in combination with TCAs or experiencing convulsions or cardiac arrhythmias, and estimated a 12% prevalence of potentially harmful use of flumazenil.[173] However, a more recent UK study indicated that where flumazenil was used to treat benzodiazepine overdose there was a low incidence of seizures.[174] Although flumazenil can be effective in reversing benzodiazepine and z-hypnotic effects,[29,175–177] as the majority of DRDs and a large proportion of drug-related hospital admissions in Scotland are due to polydrug overdoses the widespread use flumazenil would also appear to be inappropriate.[5,128]

Unexpectedly, naloxone – a short-acting opioid antagonist which can be administered by intravenous or intramuscular injection – has been used with mixed success to reverse benzodiazepine and z-hypnotic effects,[176–185] reversing overdose toxicity in benzodiazepine-only cases[178] and mixed benzodiazepine and non-opiate cases.[179,180] Studies demonstrating a lack of effect did not include benzodiazepine overdoses (Table 4).[184–186] Interestingly, the studies demonstrating a lack of effect use benzodiazepine doses at half to less than a tenth of the doses seen in overdose, and assessed naloxone response within 10 minutes post administration where on average it took 12 minutes (ranging from 5 to 20 minutes) for patients to respond.[179]

Although naloxone is known to be a specific opioid antagonist that acts competitively with opioids at opioid receptors, there is some evidence that it also possibly antagonises GABA/benzodiazepine receptor function.[187] However, further research is required to confirm or refute previous studies and clarify naloxone's mechanism of action in benzodiazepine overdose, although as already acknowledged the majority of overdoses are for polydrug use where opiates are also present.[5,128]

Clinical practice research consideration

- Is there a role for naloxone in acute benzodiazepine-type drug overdose?

Table 4 Studies involving naloxone to treat benzodiazepine-type drug intoxication

Study	Study design	Population	Drugs	BDZ and mean diazepam equivalent (mg)		Naloxone dose	Comment
Positive studies							
Sohli et al[178]	Randomised controlled	Overdose, *n*=116 28 ± 11 years old, 63% female.	BDZ only	Diazepam	149mg po	0.8mg iv	Improvement in Glasgow Coma Scale for all patients, although lorazepam group was not statistically significant (*p*=0.24)
				Clonazepam	320mg po		
				Alprazolam	180mg po		
				Lorazepam	230mg po		
Malizia et al[179]	Observational	Overdose, *n*=10 Mean 19.6 years old, range 18 to 30 years.	7 BDZ only 3 BDZ + other (1 cranial trauma, 1 barbiturate + alcohol, 1 amitriptyline + alcohol†)	Not stated		0.8mg to 2.0mg iv	Time taken to waken 5 to 20 minutes, mean 11.7 ± 4.6 minutes. Respiration increased from 8 to 15 breaths per minute within 10–15 minutes of naloxone
Jordan et al[181]	Double-blind crossover	Healthy males, 25–45 years old, *n*=6	BDZ only	Diazepam 15mg/70kg iv		Placebo (saline) or naloxone 15mg/70kg at 60 minutes and 95 minutes.	Improvement in respiration over 3 hours at significantly (*p*<0.05) quicker rate than placebo

Study	Study design	Population	Drugs	BDZ and mean diazepam equivalent (mg)	Naloxone dose	Comment
Stella et al[182]	Double-blind randomised control	Adults, 20–50 years old, *n*=136 Elective abdominal surgery.	Mixed anaesthetics	Diazepam 0.345mg/kg (20mg to 27mg) Thiorpentone 2.188mg/kg Alphaxolone 0.273mg/kg Propanidid 1.747mg/kg Ketamine 0.404mg/kg	Placebo (saline) or naloxone 0.3mg to 0.5mg iv, 5 minutes before induction	Significant reduction in unconsciousness in diazepam group receiving naloxone
Moss[180]	Case	Overdose, 46-year-old female.	Mix: diazepam, talbutal and alcohol.	Diazepam 75mg po Talbutal 120mg po	0.4mg iv	No narcotics where detected in blood samples.
Negative studies						
Christensen and Huttel[186]	Double-blind randomised control	Adults, *n*=46 Gastroscopy	BDZ only	Diazepam 33.5mg (20–50mg), *n*=22 Diazepam 35.5mg (20–60mg), *n*=24	Placebo (saline) vs. 0.4mg iv	Glasgow Coma Scale 5 min before and after administration, conscious level was not significantly different between groups (*p*=0.02)
Wolkowitz et al[184]	Double-blind placebo crossover study	Males, 18–21 years, *n*=10	BDZ only	Diazepam 0.25mg/kg (17.5mg/70kg) or placebo	1.2mg iv	Diazepam produced marked reduction in measures of cognitive functioning. Naloxone had no effect on

Study	Study design	Population	Drugs	BDZ and mean diazepam equivalent (mg)		Naloxone dose	Comment
							cognitive functioning measures.
Forster et al[185]	Randomised double-blind crossover	Healthy males, mean age 30 ± 4 years, *n*=8	BDZ only	Midazolam iv	Diazepam po	Placebo (saline) or naloxone 0.015mg/kg (1mg) iv after 5 minutes	Study period 10minutes. Respiratory effects of midazolam are poorly dose related and not reversed by naloxone
				Placebo	Nil		
				0.05mg/kg	9mg		
				0.1mg/kg	18mg		
				0.2mg/kg	35mg		
Lheureux et al[176]	Case	Overdose: 50-year-old male,	Prothipendyl and alcohol	Zolpidem 300mg (~150mg diazepam)		1mg naloxone iv	No improvement consciousness or respiratory symptoms.
Cienki and Burkhart[177]	Case	Overdose: 27-year-old male	Possible mixed flunazerine	Zopiclone 105mg to 150mg (~70mg to 100mg diazepam)		2mg naloxone iv	No effect

BDZ: benzodiazepine; po: orally; iv: intravenous.
† patient died after 60 hours, cause of death attributed to aspiration pneumonia.

Conclusion

The role of benzodiazepine-type drugs in DRDs is complicated by numerous factors including: increasing availability of unregulated benzodiazepine-type NPS of unknown content and quality; self-medicating with prescribed and/or illicit benzodiazepine-type drugs; the use of supratherapeutic megadoses and the lack of information about the metabolic and physical effects of such doses; polydrug use and polypharmacy further complicating adverse drug effects; low and high drug blood concentrations being present in DRDs; benzodiazepine-type drugs being associated with increased mortality when used at routine doses; and the real risks of short-term and long-term mental health and cognitive problems associated with routine and excessive benzodiazepine-type drug use.

However, in assessing the risks posed by benzodiazepine-type drugs, one must consider the risks of the alternatives. Therefore, a better understanding of benzodiazepine-type drug use may enable the development of appropriate strategies to reduce and minimise drug-related harms, and to replicate previous achievements associated with the withdrawal of temazepam capsules.

References

1. Davies C, Murray R, editors. *United Kingdom drug situation: Annual report to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA).* 2013 edition. London: Public Health England; 2013.

2. Paulozzi LJ. Prescription drug overdoses: A review. *Journal of Safety Research* 2012;43(4):283–9.

3. Zador D, Kidd B, Hutchinson S et al. *National investigation into drug related deaths in Scotland, 2003*. August 2005:1–93. www.gov.scot/Publications/2005/08/03161745/17507 (accessed 19/1/16).

4. Black M, Bruce M, Jay J et al. *The national confidential enquiry into methadone related deaths (Scotland) 2001*. July 2004:1–30. www.healthcareimprovementscotland.org/default.aspx?page=12378 (accessed 19/1/16).

5. Barnsdale L, Gordon R, McAuley A. *The National Drug-Related Deaths Database (Scotland) Report: Analysis of deaths occurring in 2013*. 2015 April. www.isdscotland.org/Health-Topics/Drugs-and-Alcohol-Misuse/Publications/2015-04-28/2015-04-28-NDRDD-Report.pdf (accessed 19/1/16).

6. Strang J, Seivewright N, Farrell M. Intravenous and other novel abuses of benzodiazepines: the opening of Pandora's box? *British Journal of Addiction* 1992;87(10):1373–5.

7. Hammersley R, Cassidy MT, Oliver J. Drugs associated with drug-related deaths in Edinburgh and Glasgow, November 1990 to October 1992. *Addiction* 1995;90(7):959–65.

8. Hammersley R, Stephanie. Temazepam misuse, violence and disorder. *Addiction Research* 1997;5(3):213.

9. National forum on drug-related deaths in Scotland. *Annual Report 2013*. www.sfad.org.uk/userfiles/files/NFDRD_Annual_Report_2013.pdf (accessed 19/1/16).

10. Robertson JR, Ronald PJM. Prescribing benzodiazepines to drug misusers. *The Lancet* 1992;339(8802):1169–70.

11. Strang J, Griffiths P, Abbey J, Gossop M. Survey of use of injected benzodiazepines among drug users in Britain. *BMJ* 1994;308(6936):1082.

12. McAuley A, Hecht G, Barnsdale L et al. Mortality related to novel psychoactive substances in Scotland, 2012: An exploratory study. *International Journal of Drug Policy* 2015;26(5):461–7.

13. Information Services Division Scotland. *Prescribing and medicines: Medicines used in mental health*. www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Publications/data-tables.asp?id=1146#1146 (accessed 14/10/15).

14. Committee on the Review of Medicines. Systematic review of the benzodiazepines. *BMJ* 1980;280(6218):910–12.

15. Committee on Safety of Medicines. Benzodiazepine dependence and withdrawal symptoms. *Current Problems* 1988(21):1–2.

16. Towle I, Adams J. A novel, pharmacist-led strategy to reduce the prescribing of benzodiazepines in Paisley. *Pharmaceutical Journal* 2006;276(7386): 136–8.

17. Johnson C, Thomson A. Prescribing support pharmacists support appropriate benzodiazepine and Z-drug reduction 2008/09 – experiences from North Glasgow. *Clinical Pharmacology* 2010;3(Supp 1):S5–S6.

18. Simonsen KW, Normann PT, Ceder G et al. Fatal poisoning in drug addicts in the Nordic countries in 2007. *Forensic Science International* 2011;207 (1–3):170–6.

19. Licata M, Palazzoli F, Verri P et al. Benzodiazepine misuse. Results of an Italian post-mortem study. *Heroin Addiction and Related Clinical Problems* 2013;15(1):15–20.

20. Lee D, Delcher C, Maldonado-Molina MM et al. Trends in licit and illicit drug-related deaths in Florida from 2001 to 2012. *Forensic Science International* 2014;245:178–86.

21. Chan GM, Stajic M, Marker EK et al. Testing positive for methadone and either a tricyclic antidepressant or a benzodiazepine is associated with an accidental overdose death: analysis of medical examiner data. *Academic Emergency Medicine* 2006;13(5):543–7.

22. Havens JR, Oser CB, Knudsen HK et al. Individual and network factors associated with non-fatal overdose among rural Appalachian drug users. *Drug and Alcohol Dependence* 2011;115(1–2):107–12.

23. Mikolaenko IMD, Robinson CAJPD, Davis GGMD. A review of methadone deaths in Jefferson County, Alabama. *American Journal of Forensic Medicine and Pathology* 2002;23(3):299–304.

24. Darke S, Marel C, Mills KL et al. Patterns and correlates of non-fatal heroin overdose at 11-year follow-up: Findings from the Australian Treatment Outcome Study. *Drug and Alcohol Dependence* 2014;144(0):148–52.

25. Pilgrim JL, McDonough M, Drummer OH. A review of methadone deaths between 2001 and 2005 in Victoria, Australia. *Forensic Science International* 2013;226(1–3):216–22.

26. Brayfield A, editor. *Martindale: The complete drug reference. 38th edition*. London: Pharmaceutical Press; 2014.

27. Dell'osso B, Lader M. Do benzodiazepines still deserve a major role in the treatment of psychiatric disorders? A critical reappraisal. *European Psychiatry* 2013;28(1):7–20.

28. Gunja N. The clinical and forensic toxicology of z-drugs. *Journal of Medical Toxicology* 2013;9(2):155–62.

29. Joint Formulary Committee. *British National Formulary. 69th edition*. London: BMJ Group and Pharmaceutical Press; March 2015.

30. National Institute for Health and Care Excellence. *Generalised anxiety disorder and panic disorder (with or without agoraphobia) in Adults: Management in primary, secondary and community care. Clinical Guideline 113*. London: National Institute for Health and Care Excellence; 2011.

31. Baldwin DS, Anderson IM, Nutt DJ et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association for Psychopharmacology. *Journal of Psychopharmacology* 2014;28(5):403–39.

32. Glass J, Lanctot KL, Herrmann N et al. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ* 2005;331(7526):1169.

33. Department of Health (England) and the devolved administrations (2007). *Drug Misuse and Dependence: UK Guidelines on Clinical Management*. London: Department of Health (England), the Scottish Government, Welsh Assembly Government and Northern Ireland Executive; 2007.

34. Ford C, Law F. *Guidance for the use and reduction of misuse of benzodiazepines and other hypnotics and anxiolytics in general practice*; 2014. www.smmgp.org.uk/download/guidance/guidance025.pdf (accessed 19/1/16).

35. World Health Organisation. Definition and general considerations of defined daily doses. www.whocc.no/ddd/definition_and_general_considera/ (accessed 14/10/15).

36. Siriwardena AN, Qureshi Z, Gibson S et al. GPs' attitudes to benzodiazepine and 'Z-drug' prescribing: A barrier to implementation of evidence and guidance on hypnotics. *British Journal of General Practice* 2006;56(533):964–7.

37. Siriwardena AN, Qureshi MZ, Dyas JV et al. Magic bullets for insomnia? Patients' use and experiences of newer (Z drugs) versus older (benzodiazepine) hypnotics for sleep problems in primary care. *British Journal of General Practice* 2008;58(551):417–22.

38. Ashton H. *The Ashton Manual. Benzodiazepines: how they work and how to withdraw*. www.benzo.org.uk/ (accessed 14/10/15).

39. Taylor D, Paton C, Kapur S. *The Maudsley Prescribing Guidelines in Psychiatry. 11th edition*. Chichester: Wiley-Blackwell; 2012.

40. *Scottish drug tariff, Part 7: Drugs and preparations with tariff prices*. 7/4/15. www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Scottish-Drug-Tariff/Drugs-and-Preparations-with-Tariff-Prices.asp?Co=Y (accessed 14/10/15).

41. Norman TR, Burrows GD. Plasma concentrations of benzodiazepines — A review of clinical findings and implications. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 1984;8(1):115–26.

42. eMC: electronic Medicines Compendium UK. www.medicines.org.uk/emc/ (accessed 14/10/15).

43. Maskell PD, De Paoli G, Nitin Seetohul L, Pounder DJ. Phenazepam: The drug that came in from the cold. *Journal of Forensic and Legal Medicine* 2012;19(3):122–5.

44. Stitzer ML, Griffiths RR, McLellan AT. Diazepam use among methadone maintenance patients: Patterns and dosages. *Drug and Alcohol Dependence* 1981;8(3):189–99.

45. Dwyer R. Privileging pleasure: Temazepam injection in a heroin marketplace. *International Journal of Drug Policy* 2008;19(5):367–74.

46. Jones JD, Mogali S, Comer SD. Polydrug abuse: A review of opioid and benzodiazepine combination use. *Drug and Alcohol Dependence* 2012;125(1–2):8–18.

47. Buckley NA, McManus PR. Changes in fatalities due to overdose of anxiolytic and sedative drugs in the UK (1983–1999). *Drug Safety* 2004;27(2):135–41.

48. European Monitoring Centre for Drugs and Drug Addiction. Perspectives on Drugs. *The misuse of benzodiazepines among high-risk opioid users in Europe*. 2015. www.emcdda.europa.eu/topics/pods/benzodiazepines (accessed 19/1/16).

49. Priyadarshi S. *Audit of opiate substitution therapy and co-prescribing of anxiolytic and/or hypnotic drugs, June to August 2013*. Personal correspondence May 2015.

50. Advisory Council on the Misuse of Drugs. *Z-drugs: a review of the evidence of misuse and harm*. 2013:1–29.

51. Sikdar S, Ruben SM. Zopiclone abuse among polydrug users. *Addiction* 1996;91(2):285–6.

52. Wood DM, Green JL, Le Lait M-C, Dargan PI. Misuse of prescription benzodiazepines and non-prescription sedative hypnotics ('Z drugs') in the United Kingdom. *Clinical Toxicology* 2013;51(4):319.

53. Victorri-Vigneau C, Dailly E, Veyrac G, Jolliet P. Evidence of zolpidem abuse and dependence: results of the French Centre for Evaluation and Information on Pharmacodependence (CEIP) network survey. *British Journal of Clinical Pharmacology* 2007;64(2):198–209.

54. Paparrigopoulos T, Tzavellas E, Karaiskos D, Liappas I. Intranasal zaleplon abuse. *American Journal of Psychiatry* 2008;165(11):1489–90.

55. Whitty M, Connor JO. Intra-arterial injection of zolpidem and substance misusers. *Irish Journal of Psychological Medicine* 2007;24(4):161.

56. Parish PA. The prescribing of psychotropic drugs in general practice. *Journal of the Royal College of General Practitioners* 1971;21(92 Suppl 4):1–77.

57. Guild of Healthcare Pharmacists. *Response to call for evidence: ACMD diversion and illicit supply of medicines inquiry*. 2014. www.ghp.org.uk/ContentFiles/ghpconres1406a.pdf (accessed 19/1/16).

58. Cooper GA, Seymour A, Cassidy MT, Oliver JS. A study of methadone in fatalities in the Strathclyde Region, 1991–1996. *Medicine, Science and the Law* 1999;39(3):233–42.

59. Neale J. Methadone, methadone treatment and non-fatal overdose. *Drug and Alcohol Dependence* 2000;58(1–2):117–24.

60. Strath A. *Electronic Transfer of Prescriptions (ETP) Implementation Pack to Support eAMS*. Glasgow: NHS Education for Scotland; 2008.

61. Scottish Drugs Forum. *Drug Watch. Information sheet etizolam*. Version 1.1:1–7. 2014.

62. Corkery JM, Schifano F, Ghodse AH. Phenazepam abuse in the UK: an emerging problem causing serious adverse health problems, including death. *Human Psychopharmacology* 2012;27(3):254–61.

63. Yamawaki S. The use and development of anxiolytics in Japan. *European Neuropsychopharmacology* 1999 12;9 (Supp 6):S413–19.

64. Torrance H. *Heroin adulterated with alprazolam*. Personal correspondence May 2015.

65. Isbister GK, O'Regan L, Sibbritt D, Whyte IM. Alprazolam is relatively more toxic than other benzodiazepines in overdose. *British Journal of Clinical Pharmacology* 2004;58(1):88–95.

66. Reith DM, Fountain J, McDowell R, Tilyard M. Comparison of the Fatal Toxicity Index of zopiclone with benzodiazepines. *Journal of Toxicology: Clinical Toxicology* 2003;41(7):975–80.

67. Seymour A, Black M, Jay J et al. The role of methadone in drug-related deaths in the west of Scotland. *Addiction* 2003;98(7):995–1002.

68. Woods JH, Katz JL, Winger G. Benzodiazepines: Use, abuse, and consequences. *Pharmacological Reviews* 1992;44(2):155–338.

69. Scottish Public Health Observatory. *Prescribing for opioid dependency*. 27/8/15. www.scotpho.org.uk/behaviour/drugs/data/treatment-for-drug-misuse (accessed 14/10/15).

70. Marteau D, McDonald R, Patel K. The relative risk of fatal poisoning by methadone or buprenorphine within the wider population of England and Wales. *BMJ Open* 2015;5(5).

71. Information Services Division. *CHI Number*. www.ndc.scot.nhs.uk/Dictionary-A-Z/Definitions/index.asp?Search=C&ID=128&Title=CHI (accessed 14/10/15).

72. Information Services Division. *Prescribing Information System for Scotland*. www.isdscotland.scot.nhs.uk/Health-Topics/Prescribing-and-Medicines/Prescribing-Datamarts/ (accessed 14/10/15).

73. Niwa T, Shiraga T, Ishii I et al. Contribution of human hepatic cytochrome P450 isoforms to the metabolism of psychotropic drugs. *Biological and Pharmaceutical Bulletin* 2005;28(9):1711–16.

74. Mégarbane B, Hreiche R, Pirnay S et al. Does high-dose buprenorphine cause respiratory depression?: possible mechanisms and therapeutic consequences. *Toxicological Reviews* 2006;25(2):79–85.

75. Lintzeris N, Nielsen S. Benzodiazepines, methadone and buprenorphine: interactions and clinical management. *The American Journal on Addictions* 2010;19(1):59–72.

76. Seldén T, Ahlner J, Druid H, Kronstrand R. Toxicological and pathological findings in a series of buprenorphine related deaths. Possible risk factors for fatal outcome. *Forensic Science International* 2012;220(1–3):284–90.

77. Greenblatt DJ, Harmatz JS, Von Moltke LL et al. Comparative kinetics and response to the benzodiazepine agonists triazolam and zolpidem: Evaluation of sex-dependent differences. *Journal of Pharmacology and Experimental Therapeutics* 2000;293(2):435–43.

78. Olubodun JO, Ochs HR, Von Moltke LL et al. Pharmacokinetic properties of zolpidem in elderly and young adults: Possible modulation by testosterone in men. *British Journal of Clinical Pharmacology* 2003;56(3):297–304.

79. Liston HL, Markowitz JS, DeVane CL. Drug glucuronidation in clinical psychopharmacology. *Journal of Clinical Psychopharmacology* 2001;21(5):500–15.

80. Divoll M, Greenblatt DJ, Lacasse Y, Shader RI. Benzodiazepine overdosage: Plasma concentrations and clinical outcome. *Psychopharmacology* 1981;73(4):381–3.

81. Jönsson AK, Söderberg C, Espnes KA et al. Sedative and hypnotic drugs – fatal and non-fatal reference blood concentrations. *Forensic Science International* 2014 3;236(0):138–45.

82. Brunton LL, Chabner BA, Knollmann BC. *Goodman and Gilman's The pharmacological basis of therapeutics*. 12th edition. New York, N.Y.; London: McGraw-Hill; 2011.

83. Baxter K, Preston CL, editors. *Stockley's drug interactions*. 10th edition. London: Pharmaceutical Press; 2013.

84. Häkkinen M, Launiainen T, Vuori E, Ojanperä I. Benzodiazepines and alcohol are associated with cases of fatal buprenorphine poisoning. *European Journal of Clinical Pharmacology* 2012;68(3):301–9.

85. Pirnay S, Borron SW, Giudicelli CP et al. A critical review of the causes of death among post-mortem toxicological investigations: analysis of 34 buprenorphine-associated and 35 methadone-associated deaths. *Addiction* 2004;99(8):978–88.

86. Tracqui A, Kintz P, Ludes B. Buprenorphine-related deaths among drug addicts in France: a report on 20 fatalities. *Journal of Analytical Toxicology* 1998 Oct;22(6):430–4.

87. Reynaud M, Petit G, Potard D, Courty P. Six deaths linked to concomitant use of buprenorphine and benzodiazepines. *Addiction* 1998;93(9):1385–92.

88. Bell JR, Butler B, Lawrance A et al. Comparing overdose mortality associated with methadone and buprenorphine treatment. *Drug and Alcohol Dependence* 2009;104(1–2):73–7.

89. Auriacombe M, Franques PMP, Tignol J. Deaths attributable to methadone vs buprenorphine in France. *The Journal of the American Medical Association* 2001;285(1):45.

90. Schuman-Olivier Z, Hoeppner BB, Weiss RD et al. Benzodiazepine use during buprenorphine treatment for opioid dependence: Clinical and safety outcomes. *Drug and Alcohol Dependence* 2013;132(3):580–6.

91. Fatseas M, Auriacombe M. Why buprenorphine is so successful in treating opiate addiction in France. *Current Psychiatry Reports* 2007;9(5):358–64.

92. Barbone F, McMahon AD, Davey PG et al. Association of road-traffic accidents with benzodiazepine use. *Lancet* 1998;352(9137):1331–6.

93. Gustavsen I, Bramness JG, Skurtveit S et al. Road traffic accident risk related to prescriptions of the hypnotics zopiclone, zolpidem, flunitrazepam and nitrazepam. *Sleep Medicine* 2008;9(8):818–22.

94. Sterke CS, van Beeck EF, van der Velde N et al. New insights: dose-response relationship between psychotropic drugs and falls: a study in nursing home residents with dementia. *Journal of Clinical Pharmacology* 2012;52(6):947–55.

95. Gallacher J, Elwood P, Pickering J et al. Benzodiazepine use and risk of dementia: evidence from the Caerphilly Prospective Study (CaPS). *Journal of Epidemiology and Community Health* 2012;66(10):869–73.

96. Chen PL, Lee WJ, Sun WZ et al. Risk of dementia in patients with insomnia and long-term use of hypnotics: a population-based retrospective cohort study. *PLoS ONE* 2012;7(11):e49113.

97. Billioti de Gage S, Begaud B, Bazin F et al. Benzodiazepine use and risk of dementia: prospective population based study. *British Medical Journal* 2012;345:e6231.

98. Billioti de Gage S, Moride Y, Ducruet T, et al. Benzodiazepine use and risk of Alzheimer's disease: case-control study. *British Medical Journal* 2014;349:g5205.

99. Stewart SA. The effects of benzodiazepines on cognition. *Journal of Clinical Psychiatry* 2005;66(Suppl 2):9–13.

100. Guina J, Rossetter SR, De Rhodes BJ et al. Benzodiazepines for PTSD: A systematic review and meta-analysis. *Journal of Psychiatric Practice* 2015;21(4):281–303.

101. Otto MW, Bruce SE, Deckersbach T. Benzodiazepine use, cognitive impairment, and cognitive-behavioral therapy for anxiety disorders: issues in the treatment of a patient in need. *Journal of Clinical Psychiatry* 2005;66(Suppl 2):34–8.

102. Barker MJ, Greenwood KM, Jackson M, Crowe SF. Cognitive effects of long-term benzodiazepine use: a meta-analysis. *CNS Drugs* 2004;18(1):37–48.

103. Barker MJ, Greenwood KM, Jackson M, Crowe SF. Persistence of cognitive effects after withdrawal from long-term benzodiazepine use: a meta-analysis. *Archives of Clinical Neuropsychology* 2004;19(3):437–54.

104. Mancuso CE, Tanzi MG, Gabay M. Paradoxical reactions to benzodiazepines: Literature review and treatment options. *Pharmacotherapy* 2004;24(9):1177–85.

105. Soldatos CR, Kales A, Bixler EO et al. Side effects of benzodiazepine hypnotics. *Clinical Neuropharmacology* 1985;8(Supp 1):S112–17.

106. Paton C. Benzodiazepines and disinhibition: A review. *Psychiatric Bulletin* 2002;26(12):460–2.

107. Olson LG. Hypnotic hazards: Adverse effects of zolpidem and other z-drugs. *Australian Prescriber* 2008;31(6):146–9.

108. Chopra A, Selim B, Silber MH, Krahn L. Para-suicidal amnestic behavior associated with chronic zolpidem use: Implications for patient safety. *Psychosomatics* 2013;54(5):498–501.

109. Mortaz Hejri S, Faizi M, Babaeian M. Zolpidem-induced suicide attempt: a case report. *DARU Journal of Pharmaceutical Sciences* 2013;21(1):77.

110. McBeth BD, McNamara RM, Ankel FK et al. Modafinil and zolpidem use by emergency medicine residents. *Academic Emergency Medicine* 2009;16(12):1311–17.

111. Moloney I, Bren EG, El Hassan H, Kelly BD. Extreme agitation occurring with zopiclone. *Irish Medical Journal* 2007;100(6):511.

112. Jean Louis C, Fernandez B, Beaumont C et al. A case of zaleplon overdose. *Clinical Toxicology* 2008;46(8):782.

113. Darke S, Ross J. Suicide among heroin users: rates, risk factors and methods. *Addiction* 2002;97(11):1383–94.

114. Brower KJ, McCammon RJ, Wojnar M et al. Prescription sleeping pills, insomnia, and suicidality in the National Comorbidity Survey Replication. *Journal of Clinical Psychiatry* 2011;72(4):515–21.

115. Darke S, Ross J, Lynskey M, Teesson M. Attempted suicide among entrants to three treatment modalities for heroin dependence in the Australian Treatment Outcome Study (ATOS): prevalence and risk factors. *Drug and Alcohol Dependence* 2004;73(1):1–10.

116. Kripke DF. Greater incidence of depression with hypnotic use than with placebo. *BMC Psychiatry* 2007;7:42.

117. Man L-H, Best D, Gossop M, Stillwell G, Strang J. Relationship between prescribing and risk of opiate overdose among drug users in and out of maintenance treatment. *European Addiction Research* 2004;10(1):35–40.

118. Kumagai K, Yamanouchi Y, Matsuo K et al. Antiarrhythmic and proarrhythmic properties of diazepam demonstrated by electrophysiological study in humans. *Clinical Cardiology* 1991;14(5):397–401.

119. Agelink MW, Majewski TB, Andrich J, Mueck-Weymann M. Short-term effects of intravenous benzodiazepines on autonomic neurocardiac regulation in humans: A comparison between midazolam, diazepam, and lorazepam. *Critical Care Medium* 2002;30(5):997–1006.

120. McCowan C, Kidd B, Fahey T. Factors associated with mortality in Scottish patients receiving methadone in primary care: retrospective cohort study. *British Medical Journal* 2009;338:b2225.

121. Kallergis EM, Goudis CA, Simantirakis EN et al. Mechanisms, risk factors, and management of acquired long QT syndrome: A comprehensive review. *The Scientific World Journal* 2012;2012:212178.

122. Castro VM, Clements CC, Murphy SN et al. QT interval and antidepressant use: A cross sectional study of electronic health records. *British Medical Journal* 2013;346(7894):f288.

123. Leucht S, Cipriani A, Spineli L et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: A multiple-treatments meta-analysis. *Lancet* 2013;382(9896):951–62.

124. Hser Y, Gelberg L, Hoffman V, et al. Health conditions among aging narcotics addicts: medical examination results. *Journal of Behavioral Medicine* 2004;27(6):607–22.

125. Nyhlen A, Fridell M, Backstrom M, Hesse M, Krantz P. Substance abuse and psychiatric co-morbidity as predictors of premature mortality in Swedish drug abusers – a prospective longitudinal study 1970–2006. *BMC Psychiatry* 2011;11.

126. Beynon CM, McVeigh J. The role of substance use in non-drug related deaths: a cross-sectional study of drug treatment clients in the North West of England. *Journal of Substance Use* 2007;12(1):39–47.

127. European Monitoring Centre for Drugs and Drug Addiction. *Polydrug Use: Patterns and Responses*. 2009. www.emcdda.europa.eu/attachements.cfm/att_93217_EN_EMCDDA_SI09_polydrug%20use.pdf (accessed 19/1/16).

128. Information Services Division Scotland. *Drug-Related Hospital Statistics Scotland 2013/14 (revision).* 2014. www.isdscotland.org/Health-Topics/Drugs-and-Alcohol-Misuse/Publications/2014-10-28/2014-10-28-DrugsHospitalStatistics-Report.pdf (accessed 19/1/16).

129. Koski A, Ojanperä I, Vuori E. Alcohol and benzodiazepines in fatal poisonings. *Alcohol, Clinical and Experimental Research* 2002;26(7):956–9.

130. Darke S, Deady M, Duflou J. Toxicology and characteristics of deaths involving zolpidem in New South Wales, Australia 2001–2010. *Journal of Forensic Sciences* 2012;57(5):1259–62.

131. Zosel A, Osterberg EC, Mycyk MB. Zolpidem misuse with other medications or alcohol frequently results in Intensive Care Unit admission. *American Journal of Therapeutics* 2011;18(4):305–8.

132. Perry AE, Neilson M, Martyn-St James M et al. Pharmacological interventions for drug-using offenders. *Cochrane Database of Systematic Reviews* 2013;12:010862.

133. Sporer KA. Strategies for preventing heroin overdose. *British Medical Journal* 2003;326(7386):442–4.

134. Setanoians M, Hill D, Conroy S. *Benzodiazepine prescribing within Drug and Alcohol Services in NHS Lanarkshire (NHSL). 2014.* Personal correspondence May 2015.

135. Peles E, Linzy S, Kreek MJ, Adelson D, M. Prospective study of QTc changes among former opiate addicts since admission to methadone maintenance treatment. *Journal of Addiction Medicine* 2013;7(6):428–34.

136. Mijatovic V, Dickov A, Petkovic S et al. Safety assessment of low doses of methadone in combination with benzodiazepines in real occasions during methadone maintenance treatment - a pilot study. *Heroin Addiction and Related Clinical Problems* 2013;15(3):29–34.

137. Pani PP, Trogu E, Maremmani I, Pacini M. QTc interval screening for cardiac risk in methadone treatment of opioid dependence. *The Cochrane database of systematic reviews* 2013;6:008939.

138. Othong R, Devlin JJ, Kazzi ZN. Medical toxicologists' practice patterns regarding drug-induced QT prolongation in overdose patients: A survey in the United States of America, Europe, and Asia Pacific region. *Clinical Toxicology* 2015;53(4):204–9.

139. Anderson IM, Ferrier IN, Baldwin RC et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines. *Journal of Psychopharmacology* 2008;22(4):343–396.

140. Lee SC, Klein-Schwartz W, Doyon S, Welsh C. Comparison of toxicity associated with nonmedical use of benzodiazepines with buprenorphine or methadone. *Drug and Alcohol Dependence* 2014;138:118–23.

141. Mason J, Freemantle N, Eccles M. Fatal toxicity associated with antidepressant use in primary care. *The British Journal of General Practice* 2000;50(454):366–70.

142. Jones AW, Holmgren A, Ahlner J. Blood methadone concentrations in living and deceased persons: Variations over time, subject demographics, and relevance of coingested drugs. *Journal of Analytical Toxicology* 2012;36(1):12–18.

143. Stenhouse G, Stephen D, Grieve JHK. Blood free morphine levels vary with concomitant alcohol and benzodiazepine use. *Journal of Clinical Forensic Medicine* 2004;11(6):285–8.

144. Information Services Division. Summary: Age Demographics. 2013. www.gov.scot/Topics/People/Equality/Equalities/DataGrid/Age/AgePopMig (accessed 14/10/15).

145. Information Services Division. Estimating the National and Local Prevalence of Problem Drug Use in Scotland 2012/13. 2014. https://isdscotland.scot.nhs.uk/Health-Topics/Drugs-and-Alcohol-Misuse/Publications/2014-10-28/2014-10-28-Drug-Prevalence-Report.pdf?54406374693 (accessed 14/10/15).

146. Information Services Division. Scottish Drugs Misuse Database (SDMD): NHS Health Board Overview of Initial Assessments for Specialist Drug Treatment 2012/13. 2014. https://isdscotland.scot.nhs.uk/Health-Topics/Drugs-and-Alcohol-Misuse/Publications/2014-06-24/2014-06-24-SDMD-Report.pdf?30750674010 (accessed 14/10/15).

147. Barnett K, Mercer SW, Norbury M et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012;380(9836):37–43.

148. Pirmohamed M, James S, Meakin S et al. Adverse drug reactions as cause of admission to hospital: Prospective analysis of 18 820 patients. *British Medical Journal* 2004;329(7456):15–19.

149. Howard RL, Avery AJ, Slavenburg S et al. Which drugs cause preventable admissions to hospital? A systematic review. *British Journal of Clinical Pharmacology* 2007;63(2):136–47.

150. Lugoboni F, Carli S, Bissoli G et al. Evaluation of the quality of life in 171 patients undergoing methadone maintenance treatment and in 46 monodependent benzodiazepine patients. *Heroin Addiction and Related Clinical Problems* 2014;16(4):5–14.

151. Firoz SMD, Carlson GBA. Characteristics and treatment outcome of older methadone-maintenance patients. *The American Journal of Geriatric Psychiatry* 2004;12(5):539–41.

152. Kumar PJ, Clark ML. *Clinical medicine: a textbook for medical students and doctors. 4th edition*. Edinburgh: WB Saunders; 1998.

153. Langer RD, Kripke DF, Kline LE. Short-acting hypnotic drugs increase mortality and obese patients are particularly vulnerable. *Circulation* 2012;125(10 Supp 1):Abstract 052.

154. Glass JR, Sproule BA, Herrmann N, Busto UE. Effects of 2-week treatment with temazepam and diphenhydramine in elderly insomniacs: a randomized, placebo-controlled trial. *Journal of Clinical Psychopharmacology* 2008;28(2):182–8.

155. Huedo-Medina TB, Kirsch I, Middlemass J et al. Effectiveness of non-benzodiazepine hypnotics in treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration. *British Medical Journal* 2012;345:e8343.

156. Hjorthøj C, Østergaard MLD, Benros ME et al. Association between alcohol and substance use disorders and all-cause and cause-specific mortality in schizophrenia, bipolar disorder, and unipolar depression: a nationwide, prospective, register-based study. *Lancet Psychiatry* 2015;2(9):801–8.

157. Weich S, Pearce HL, Croft P et al. Effect of anxiolytic and hypnotic drug prescriptions on mortality hazards: retrospective cohort study. *British Medical Journal* 2014;348:g1996.

158. Johnson CF, Dougall NJ, Williams B et al. Patient factors associated with SSRI dose for depression treatment in general practice: a primary care cross sectional study. *BMC Family Practice* 2014;15:210.

159. Petty DR, House A, Knapp P, Raynor T, Zermansky A. Prevalence, duration and indications for prescribing of antidepressants in primary care. *Age and Ageing* 2006;35(5):523–6.

160. Mitchell AJ, Vaze A, Rao S. Clinical diagnosis of depression in primary care: a meta-analysis. *Lancet* 2009;374(9690):609–19.

161. Park TW, Nelson K, Xuan Z et al. The association between benzodiazepine prescription and aberrant drug behaviors in primary care patients receiving chronic opioid therapy. *Drug and Alcohol Dependence* 2015;146:e61–2.

162. Tsimtsiou Z, Ashworth M, Jones R. Variations in anxiolytic and hypnotic prescribing by GPs: a cross-sectional analysis using data from the UK Quality and Outcomes Framework. *British Journal of General Practice* 2009;59(563):e191–8.

163. Charlson F, Degenhardt L, McLaren J, Hall W, Lynskey M. A systematic review of research examining benzodiazepine-related mortality. *Pharmacoepidemiology and Drug Safety* 2009;18(2):93–103.

164. Jaussent I, Ancelin ML, Berr C et al. Hypnotics and mortality in an elderly general population: a 12-year prospective study. *BMC Medicine* 2013;11:212.

165. Obiora E, Hubbard R, Sanders RD, Myles PR. The impact of benzodiazepines on occurrence of pneumonia and mortality from pneumonia: a nested case-control and survival analysis in a population-based cohort. *Thorax* 2013;68(2):163–70.

166. Frie C, Johnson CF, Akram G, Downes N, McTaggart S. *A national study of anxiolytic and hypnotic prescribing in people 65 years and older in Scotland*. [dissertation]. University of Strathclyde; 2014.

167. Strang J, Griffiths P, Powis B et al. Which drugs cause overdose among opiate misusers? Study of personal and witnessed overdoses. *Drug Alcohol Review* 1999;18(3):253–61.

168. Walley AY, Xuan Z, Hackman HH et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: Interrupted time series analysis. *British Medical Journal* 2013;346 (7894): f174.

169. Weinbroum AA, Flaishon R, Sorkine P, Szold O, Rudick V. A risk-benefit assessment of flumazenil in the management of benzodiazepine overdose. *Drug Safety* 1997;17(3):181–96.

170. Krayeva YV, Brusin KM, Bushuev AV et al. Pre-hospital management and outcome of acute poisonings by ambulances in Yekaterinburg, Russia. *Clinical Toxicology* 2013;51(8):752–60.

171. Association of Ambulance Chief Executives and Joint Royal Colleges Ambulance Liaison Committee. *UK Ambulance Services Clinical Practice Guidelines 2013*. http://aaceguidelines.co.uk/ (accessed 19/1/16).

172. Eaton CJ. *Essentials of immediate medical care. 2nd edition*. Edinburgh: Churchill Livingstone; 1999.

173. Mathieu-Nolf M, Babe MA, Coquelle-Couplet V et al. Flumazenil use in an emergency department: A survey. *Journal of Toxicology: Clinical Toxicology* 2001;39(1):15–20.

174. Veiraiah A, Dyas J, Cooper G, Routledge PA, Thompson JP. Flumazenil use in benzodiazepine overdose in the UK: A retrospective survey of NPIS data. *Emergency Medicine Journal* 2012;29(7):565–9.

175. Chen-Chang Yang, Juo-Fang Deng. Utility of flumazenil in zopiclone overdose. *Clinical Toxicology* 2008;46(9):920–1.

176. Lheureux P, Debailleul G, De Witte O, Askenasi R. Zolpidem intoxication mimicking narcotic overdose: Response to flumazenil. *Human and Experimental Toxicology* 1990;9(2):105–7.

177. Cienki JJ, Burkhart KK, Donovan JW. Zopiclone overdose responsive to flumazenil. *Clinical Toxicology* 2005;43(5):385–6.

178. Solhi H, Mostafazadeh B, Vishteh HRK, Ghezavati AR, Shooshtarizadeh A. Benefit effect of naloxone in benzodiazepines intoxication: findings of a preliminary study. *Human and Experimental Toxicology* 2011;30(7):535–40.

179. Malizia E, Cerbo R, Ambrosini M. Naloxone treatment of acute alcoholic or benzodiazepine intoxication. *Journal of Applied Toxicology* 1982;2(1):39–41.

180. Moss LM. Naloxone reversal of non-narcotic induced apnea. *Journal of the American College of Emergency Physicians* 1973;2(1):46–8.

181. Jordan C, Lehane JR, Jones JG. Respiratory depression following diazepam: reversal with high-dose naloxone. *Anesthesiology* 1980;53(4):293–8.

182. Stella L, Crescenti A, Torri G. Effect of naloxone on the loss of consciousness induced by i.v. anaesthetic agents in man. *British Journal of Anaesthesia* 1984;56(4):369–73.

183. Duka T, Millan MJ, Ulsamer B, Doenicke A. Naloxone attenuates the anxiolytic action of diazepam in man. *Life Sciences* 1982;31(16–17):1833–6.

184. Wolkowitz OM, Tinklenberg JR. Naloxone's effect on cognitive functioning in drug-free and diazepam-treated normal humans. *Psychopharmacology* 1985;85(2):221–3.

185. Forster, Alain M, Denis B, Marlies G, Marcel. Respiratory depressant effects of different doses of midazolam and lack of reversal with naloxone – a double-blind randomized study. *Anesthesia & Analgesia* 1983;62(10):920–4.

186. Christensen KN Huttel M. Naloxone does not antagonize diazepam-induced sedation. *Anesthesiology* 1979;51(2):187.

187. Yuan W, Williams BN. Use of naloxone in the treatment of benzodiazepine poisoning. *Human and Experimental Toxicology* 2012;31(4):406–7.

Glossary

Term	Definition
ADE	Adverse drug effect
Agonist	Drug which attaches to a receptor producing the same effect to the body's natural molecule
Antagonist	Drug which attaches to a receptor interfering with or preventing the body's natural agonist effect
Benzo-burden	Benzodiazepine-type drug use includes dose, drug potency, frequency of use, exposure, etc.
Benzos	Benzodiazepine-type drugs
Blues	Blue diazepam (valium) 10mg tablets
CNS	Central nervous system
DDD	Defined daily doses
DDD/1000 population	Defined daily doses per 1000 population. Using mid-year population estimates from General Registrar's Office for Scotland
Drug half-life	The time taken for drug blood concentrations to reduce by 50%
GABA	Gamma-aminobutyric acid – an inhibitory neurotransmitter
Items	Prescriptions
Megadose	Large dose outwith the licensed dose
NPS	New or Novel Psychoactive Substance
Paradoxical effects	Effects similar to those the drugs are being used to treat
Pharmacodynamics	Study of how the effects of drugs are enhanced or diminished in the presence of other drugs
Pharmacokinetics	Study of how drugs are absorbed into, distributed, broken down in and excreted from the body

Term	Definition
Polydrug	Multiple drug; commonly used to described multiple drug use
Polypharmacy	Multiple prescribed drug use
QTc	QT interval corrected. Prolonged QTc increases the risk of sudden cardiac death from heart arrhythmias, such as ventricular tachycardias

Appendix 1 – Anxiolytic and hypnotic prescribing data Scotland

Figures developed from Information Services Division Scotland prescribing data.[q13]

[q] World Health Organisation DDDs are defined as ‘the assumed average maintenance dose per day for a drug used for its main indication in adults’ and do not necessarily reflect the recommended or prescribed daily dose. Instead they provide a standardised method to compare prescribing volumes between organisations.[35]

Figure 2 Anxiolytic and hypnotic DDDs per 1000 population per day by Scottish Health Board.

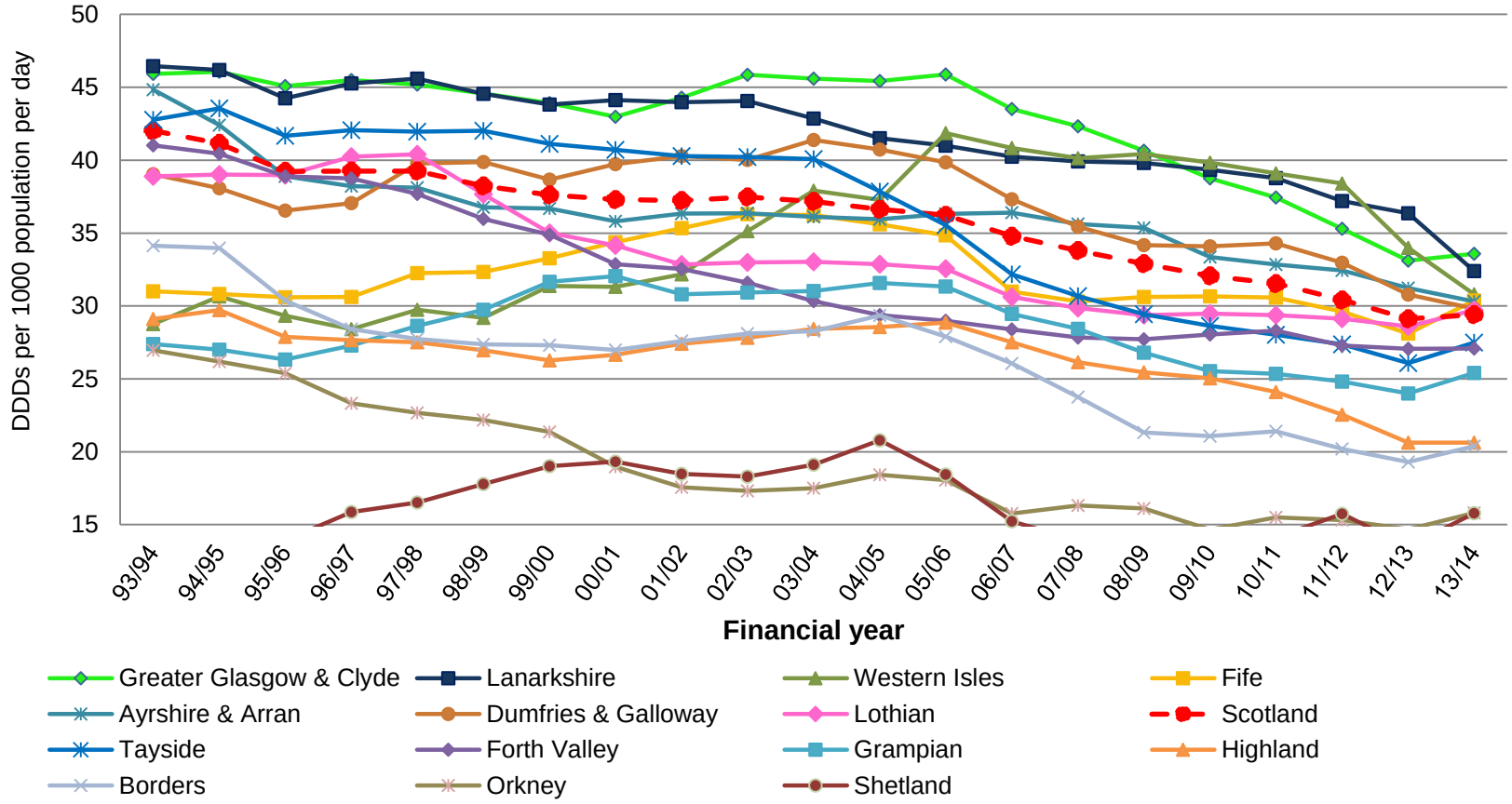


Figure 3 Anxiolytic and hypnotic prescriptions (items) and DDDs per 1000 population per day by financial year for Scotland.

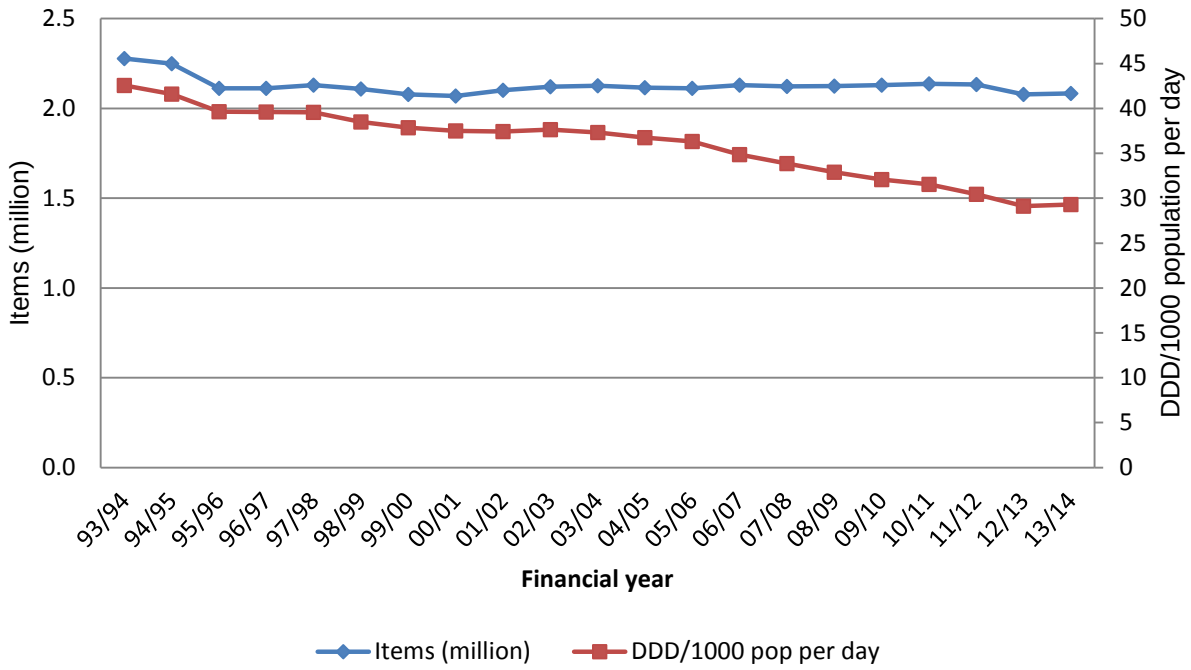
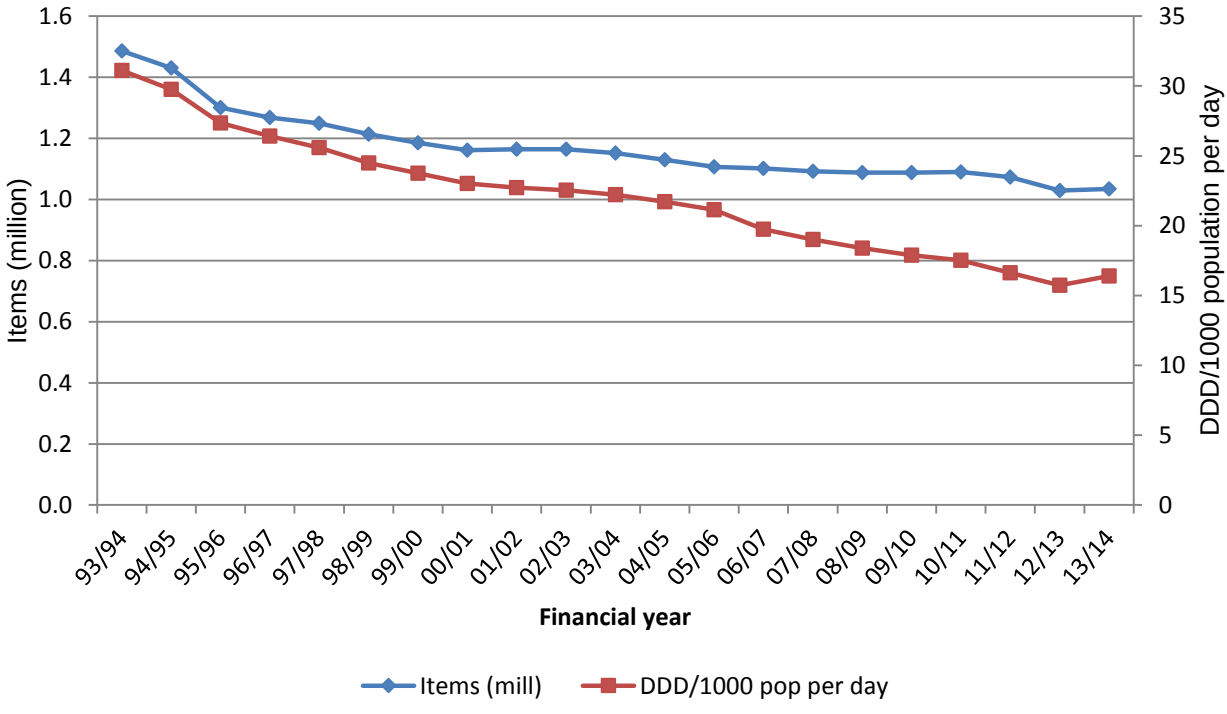
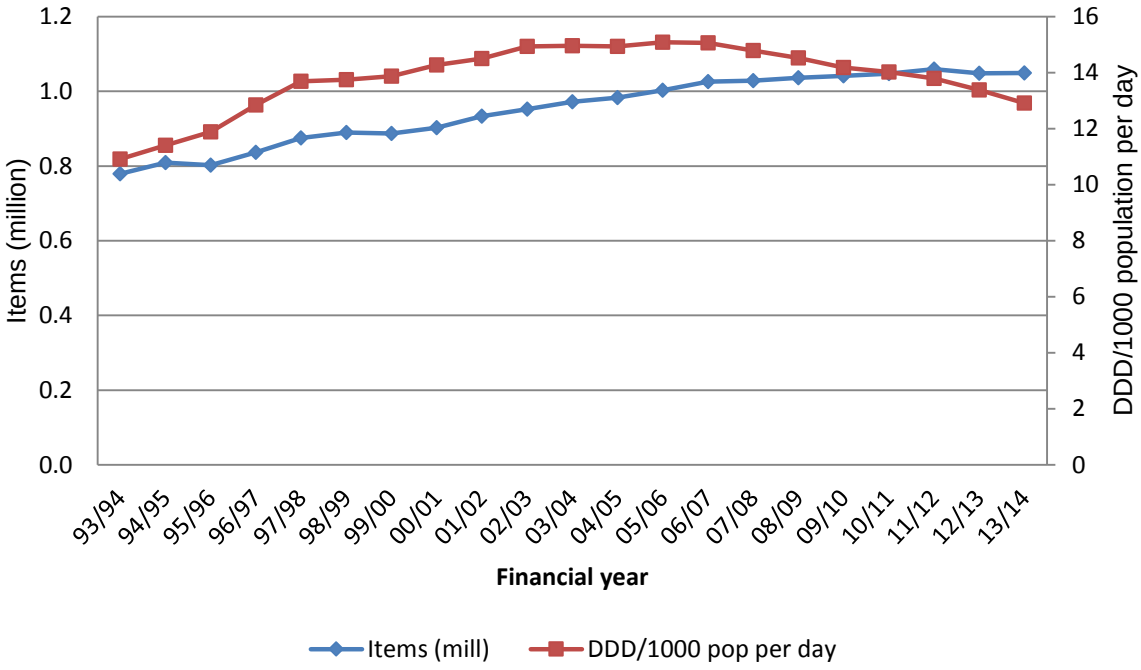


Figure 4 Hypnotic prescriptions (items) and DDDs per 1000 population per day, by financial year for Scotland.



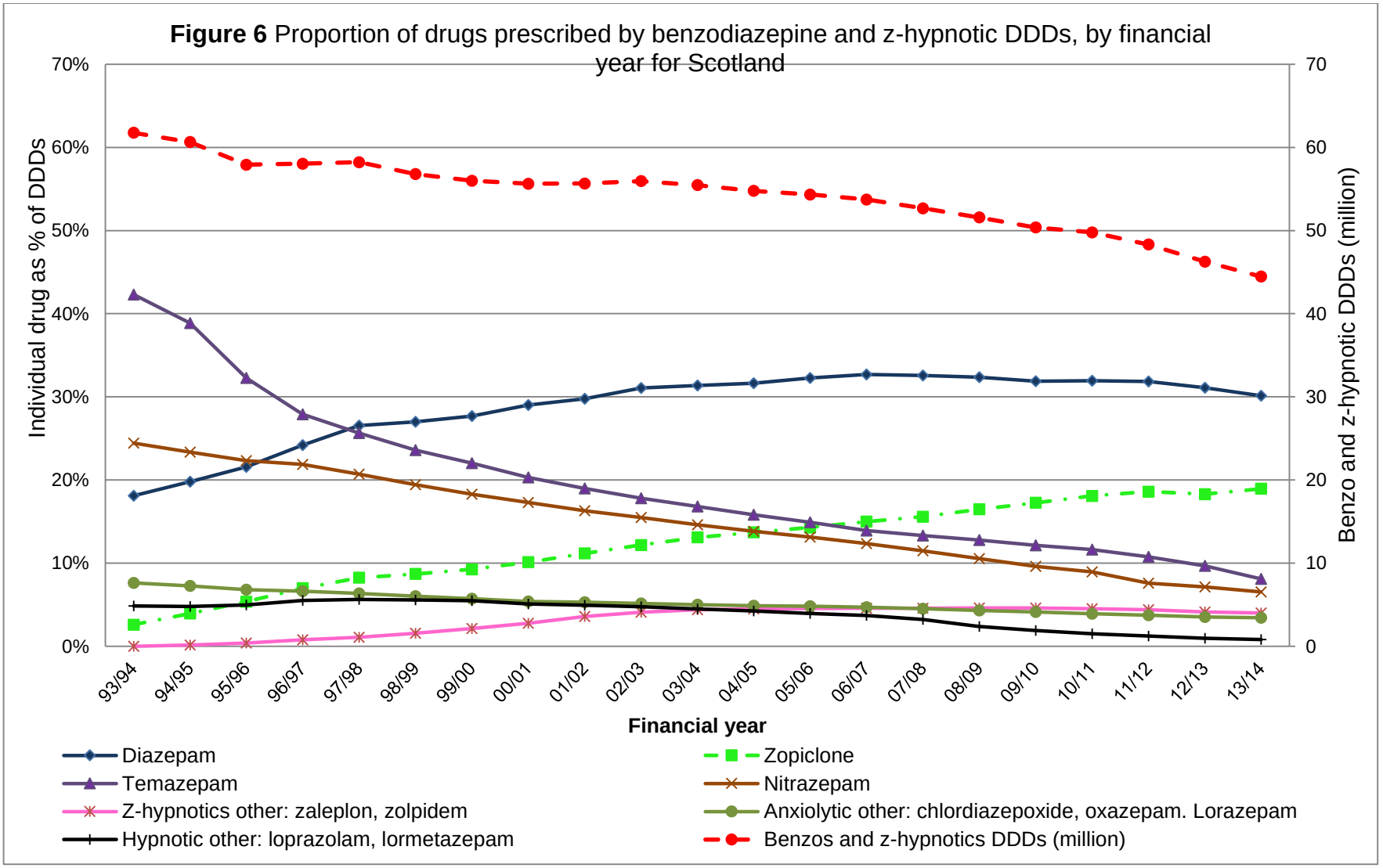
Note: prescription (items) numbers diverging from DDDs/1000 population per day indicates that prescribers are issuing smaller quantities of anxiolytics and hypnotics on individual prescriptions, e.g. 28-day prescriptions instead of 56-day prescriptions, 28 day prescription with 28 tablets instead of 56 tablets.

Figure 5 Anxiolytic prescriptions (items) and DDDs per 1000 population per day, by financial year for Scotland.



Note: Diazepam accounts for the majority of anxiolytics prescribed, but it is also used for benzodiazepine and z-hypnotic withdrawal, which will partially account for the observed increase in anxiolytic DDDs/1000 population per day.

Figure 6 Proportion of drugs prescribed by benzodiazepine and z-hypnotic DDDs, by financial year for Scotland



Appendix 2 – Literature search strategy

Benzodiazepines: Medline 1970 to March 2015

#	Search	Actions	Search type
1	alprazolam.mp. or exp Alprazolam/	2214	Advanced
2	bromazepam.mp. or exp Bromazepam/	501	Advanced
3	brotizolam.mp.	196	Advanced
4	chlordiazepoxide.mp. or exp Chlordiazepoxide/	4507	Advanced
5	clobazam.mp.	672	Advanced
6	clonazepam.mp. or exp Clonazepam/	3680	Advanced
7	Clorazepate Dipotassium/ or clorazepate.mp.	447	Advanced
8	cloxazolam.mp.	33	Advanced
9	delorazepam.mp.	16	Advanced
10	exp Diazepam/ or diazepam.mp.	23355	Advanced
11	estazolam.mp. or exp Estazolam/	161	Advanced
12	etizolam.mp.	76	Advanced
13	flunitrazepam.mp. or exp Flunitrazepam/	3565	Advanced
14	flurazepam.mp. or exp Flurazepam/	1126	Advanced
15	halazepam.mp.	57	Advanced
16	ketazolam.mp.	34	Advanced
17	loprazolam.mp.	71	Advanced
18	lorazepam.mp. or exp Lorazepam/	3748	Advanced
19	lormetazepam.mp.	233	Advanced
20	medazepam.mp. or exp Medazepam/	243	Advanced
21	nitrazepam.mp. or exp Nitrazepam/	1186	Advanced

22	nordazepam.mp. or exp Nordazepam/	496	Advanced
23	midazolam.mp. or exp Midazolam/	10626	Advanced
24	oxazolam.mp.	28	Advanced
25	oxazepam.mp. or exp Oxazepam/	1717	Advanced
26	phenazepam.mp.	290	Advanced
27	pinazepam.mp.	36	Advanced
28	prazepam.mp. or exp Prazepam/	208	Advanced
29	quazepam.mp.	142	Advanced
30	temazepam.mp. or exp Temazepam/	961	Advanced
31	tofisopam.mp.	107	Advanced
32	triazolam.mp. or exp Triazolam/	1624	Advanced
33	zolazepam.mp. or exp Zolazepam/	318	Advanced
34	exp Benzodiazepines/ or exp Benzodiazepinones/ or benzodiazepin$.mp.	68636	Advanced
35	hypnotic$.mp. or exp "Hypnotics and Sedatives"/	110483	Advanced
36	anxiolytic$.mp. or exp Anti-Anxiety Agents/	61828	Advanced
37	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36	167647	Advanced
38	exp Mortality/ or exp Mortality, Premature/ or mortality.mp.	643133	Advanced
39	exp Death/ or death$.mp. or exp Death, Sudden/ or exp "Cause of Death"/	646334	Advanced
40	poisoning$.mp. or exp Poisoning/	159772	Advanced
41	drug related death$.mp.	490	Advanced
42	drug associated death$.mp.	13	Advanced
43	drug related mortality.mp.	78	Advanced
44	drug associated mortality.mp.	1	Advanced

45	benzodiazepine related death$.mp.	1	Advanced
46	benzodiazepine associated death$.mp.	0	Advanced
47	benzodiazepine related mortality.mp.	1	Advanced
48	benzodiazepine associated mortality.mp.	0	Advanced
49	38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48	1272296	Advanced
50	adult.mp. or exp Adult/	5988891	Advanced
51	elderly.mp. or exp Aged/	2427405	Advanced
52	exp "Aged, 80 and over"/ or older people.mp.	649251	Advanced
53	50 or 51 or 52	6009070	Advanced
54	37 and 49 and 53	4869	Advanced
55	limit 54 to (english language and humans and yr="1970 - Current")	3681	Advanced
56	exp Child, Preschool/ or exp Infant, Newborn/ or exp Child/ or paediatric$.mp. or exp Infant/	2047455	Advanced
57	55 not 56	3272	Advanced
58	exp Epilepsy, Generalized/ or exp Epilepsy, Temporal Lobe/ or exp Epilepsy, Benign Neonatal/ or exp Epilepsy, Partial, Motor/ or exp Epilepsy, Post-Traumatic/ or exp Epilepsy, Reflex/ or exp Epilepsy, Tonic-Clonic/ or epilepsy.mp. or exp Epilepsy, Partial, Sensory/ or exp Epilepsy, Absence/ or exp Epilepsy, Complex Partial/ or exp Epilepsy/ or exp Epilepsy, Rolandic/ or exp Myoclonic Epilepsy, Juvenile/ or exp Epilepsy, Frontal Lobe/	142472	Advanced
59	epileptic.mp.	28245	Advanced
60	Seizures/	42214	Advanced
61	exp Electroconvulsive Therapy/ or ect.mp.	11196	Advanced
62	exp Alcohol Withdrawal Delirium/ or alcohol withdrawal.mp.	3748	Advanced
63	exp Alcohol Withdrawal Delirium/ or alcohol withdrawal.mp.	3748	Advanced
64	exp Neuroleptic Malignant Syndrome/ or exp Serotonin Syndrome/ or acute serotonin syndrome.mp.	2454	Advanced

65	palliative care.mp. or exp Palliative Care/	44486	Advanced
66	terminal care.mp. or exp Terminal Care/	41871	Advanced
67	mechanical ventilation.mp. or exp Respiration, Artificial/	71729	Advanced
68	critical care.mp. or exp Critical Care/	52786	Advanced
69	perioperative.mp. or exp Perioperative Care/ or exp Perioperative Period/	212845	Advanced
70	premedication.mp. or exp Premedication/	26080	Advanced
71	exp Postoperative Care/ or exp Postoperative Period/ or postoperative.mp.	575519	Advanced
72	58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71	1009043	Advanced
73	57 not 72	2278	Advanced
74	from 73 keep 4, 6, 19, 21-22, 43, 46-47...	255	Advanced
75	from 74 keep 1-2, 4-6, 9, 11, 14-15, 18-26...	164	Advanced

Benzodiazepines: Embase 1970 to March 2015.

#	**Search**	**Results**	**Search type**
1	alprazolam.mp. or exp alprazolam/	15878	Advanced
2	bromazepam.mp. or exp bromazepam/	3136	Advanced
3	exp chlordiazepoxide/ or chlordiazepoxide.mp.	12228	Advanced
4	clobazam.mp. or exp clobazam/	5214	Advanced
5	clonazepam.mp. or exp clonazepam/	21387	Advanced
6	exp clorazepate dipotassium/ or clorazepate.mp. or exp clorazepate/ or exp clorazepate potassium/	3836	Advanced
7	cloxazolam.mp. or exp cloxazolam/	235	Advanced
8	delorazepam.mp. or exp delorazepam/	360	Advanced
9	diazepam.mp. or exp diazepam/	69908	Advanced

#	Search	Results	Search type
10	brotizolam.mp. or exp brotizolam/	846	Advanced
11	estazolam.mp. or exp estazolam/	1093	Advanced
12	etizolam.mp. or exp etizolam/	387	Advanced
13	flunitrazepam.mp. or exp flunitrazepam/	8597	Advanced
14	flurazepam.mp. or exp flurazepam/	4714	Advanced
15	halazepam.mp. or exp halazepam/	356	Advanced
16	ketazolam.mp. or exp ketazolam/	322	Advanced
17	loprazolam.mp. or exp loprazolam mesilate/ or exp loprazolam/	382	Advanced
18	lorazepam.mp. or exp lorazepam/	21932	Advanced
19	lormetazepam.mp. or exp lormetazepam/	1356	Advanced
20	medazepam.mp. or exp medazepam/	1304	Advanced
21	nitrazepam.mp. or exp nitrazepam/	6432	Advanced
22	nordazepam,.mp. or exp nordazepam/	2085	Advanced
23	exp midazolam maleate/ or exp midazolam/ or midazolam.mp.	36299	Advanced
24	oxazolam.mp. or exp oxazolam/	178	Advanced
25	oxazepam.mp. or exp oxazepam/	7837	Advanced
26	phenazepam.mp. or exp phenazepam/	462	Advanced
27	pinazepam.mp. or exp pinazepam/	117	Advanced
28	prazepam.mp. or exp prazepam/	1371	Advanced
29	quazepam.mp. or exp quazepam/	635	Advanced
30	temazepam.mp. or exp temazepam/	5284	Advanced
31	tofisopam.mp. or exp tofisopam/	343	Advanced
32	triazolam.mp. or exp triazolam/	5707	Advanced

#	Search	Results	Search type
33	exp zolazepam/ or zolazepam.mp.	463	Advanced
34	exp benzodiazepine derivative/ or benzodiazepine.mp. or exp benzodiazepine/	163842	Advanced
35	anxiolytic$.mp. or exp anxiolytic agent/	169107	Advanced
36	hypnotic$.mp. or exp hypnotic agent/	29941	Advanced
37	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36	262239	Advanced
38	mortality/	558573	Advanced
39	mortality cause.mp. or exp "cause of death"/	75926	Advanced
40	death$.mp. or exp death/	1031011	Advanced
41	poisoning.mp. or exp intoxication/	355270	Advanced
42	overdose.mp.	27147	Advanced
43	exp drug fatality/ or drug related death$.mp. or exp drug intoxication/	37887	Advanced
44	exp drug overdose/ or drug associated death$.mp.	17603	Advanced
45	drug related mortality.mp.	113	Advanced
46	drug associated mortality.mp.	2	Advanced
47	benzodiazepine related death$.mp.	0	Advanced
48	benzodiazepine associated death$.mp.	0	Advanced
49	benzodiazepine related mortality.mp.	2	Advanced
50	benzodiazepine associated mortality.mp.	0	Advanced
51	38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50	1767881	Advanced
52	37 and 51	34297	Advanced

#	Search	Results	Search type
53	limit 52 to (human and english language and yr="1970 - Current")	23182	Advanced
54	child/	1344716	Advanced
55	newborn/	482833	Advanced
56	infant/	530419	Advanced
57	54 or 55 or 56	1938660	Advanced
58	53 not 57	21104	Advanced
59	exp epilepsy/	182457	Advanced
60	epileptic$.mp.	68408	Advanced
61	seizure$.mp. or exp withdrawal seizure/ or exp seizure/	174908	Advanced
62	seizure$.mp. or exp withdrawal seizure/ or exp seizure/ or exp "seizure, epilepsy and convulsion"/	300234	Advanced
63	ect.mp. or exp electroconvulsive therapy/	19085	Advanced
64	alcohol withdrawal.mp. or exp alcohol withdrawal/	7141	Advanced
65	alcohol withdrawal delerium.mp.	0	Advanced
66	palliative care.mp. or exp palliative therapy/	74385	Advanced
67	terminal care.mp. or exp terminal care/	49478	Advanced
68	intensive care.mp. or exp intensive care/	566773	Advanced
69	exp artificial ventilation/	130740	Advanced
70	cpap.mp. or exp positive end expiratory pressure/	37451	Advanced
71	exp surgery/ or exp perioperative period/ or perioperative.mp.	3587176	Advanced
72	59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71	4352732	Advanced
73	58 not 72	10408	Advanced
74	antipsychotic$.mp. or exp neuroleptic agent/	237145	Advanced

#	Search	Results	Search type
75	premedication.mp. or exp premedication/	68826	Advanced
76	barbiturate$.mp. or exp barbituric acid derivative/	137478	Advanced
77	exp organic solvent/ or exp solvent/ or solvent$.mp.	462779	Advanced
78	glycol$.mp. or exp glycol/	145281	Advanced
79	exp anesthesia induction/ or exp propofol infusion syndrome/ or exp anesthesia/ or exp propofol/ or exp intravenous anesthesia/	293201	Advanced
80	exp isoflurane/ or exp anesthesia/ or exp halothane/	296323	Advanced
81	exp pregabalin/	8181	Advanced
82	exp gabapentin enacarbil/ or exp gabapentin/	21744	Advanced
83	exp sclerosis/	29533	Advanced
84	exp rheumatology/	44160	Advanced
85	exp autoimmune disease/ or autoimmune.mp.	513354	Advanced
86	cancer.mp. or exp neoplasm/	3812832	Advanced
87	74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86	5439874	Advanced
88	73 not 87	4680	Advanced
89	from 88 keep 14, 22, 40, 42, 50, 55-57...	477	Advanced
90	from 89 keep 1, 3-9, 11-19, 21, 23-24, 26-27...	273	Advanced

Z-hypnotic: Medline 1970 to March 2015

#	Search	Results	Search type
1	zopiclone.mp.	853	Advanced
2	zolpidem.mp.	1816	Advanced
3	zaleplon.mp.	300	Advanced

#	Search	Results	Search type
4	zaleplone.mp.	6	Advanced
5	1 or 2 or 3 or 4	2505	Advanced
6	exp Mortality/ or mortality.mp. or exp Mortality, Premature/	656531	Advanced
7	exp Death/ or exp "Cause of Death"/ or death$.mp. or exp Death, Sudden/	658216	Advanced
8	exp Poisoning/ or poisoning$.mp.	161322	Advanced
9	drug related death$.mp.	495	Advanced
10	drug associated death$.mp.	13	Advanced
11	drug related mortality.mp.	79	Advanced
12	drug associated mortality.mp.	1	Advanced
13	z-hypnotic associated death$.mp.	0	Advanced
14	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	1295832	Advanced
15	5 and 14	121	Advanced
16	limit 15 to (english language and humans and yr="1970 - Current")	91	Advanced
17	exp Infant, Newborn/ or exp Child, Preschool/ or exp Child/ or paediatric$.mp.	1949313	Advanced
18	16 not 17	83	Advanced
19	from 18 keep 1-3, 6-9, 12-13, 20, 22, 25-26...	43	Advanced

Z-hypnotic: Embase 1970 to March 2015

#	Search	Results	Search type
1	exp zopiclone/	3368	Advanced
2	exp zolpidem tartrate/ or exp zolpidem/	6758	Advanced
3	zalpelon.mp.	2	Advanced

#	Search	Results	Search type
4	exp zaleplon/	1553	Advanced
5	zaleplone.mp.	11	Advanced
6	z-hypnotic$.mp.	41	Advanced
7	1 or 2 or 3 or 4 or 5 or 6	9080	Advanced
8	exp mortality/	765640	Advanced
9	mortality cause.mp. or exp "cause of death"/	82212	Advanced
10	death$.mp. or exp death/	1121553	Advanced
11	poisoning$.mp. or exp intoxication/	390528	Advanced
12	overdose.mp.	28141	Advanced
13	exp drug fatality/ or drug related death$.mp. or exp drug intoxication/	39372	Advanced
14	drug associated death$.mp.	16	Advanced
15	drug related mortality.mp.	120	Advanced
16	drug associated mortality.mp.	3	Advanced
17	z-hypnotic associated death$.mp.	0	Advanced
18	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	2024565	Advanced
19	7 and 18	1251	Advanced
20	limit 19 to (human and english language and yr="1970 -Current")	1050	Advanced
21	child/	1483162	Advanced
22	newborn/	518213	Advanced
23	infant/	576234	Advanced
24	21 or 22 or 23	2125845	Advanced
25	20 not 24	1011	Advanced
26	from 25 keep 7, 11, 15, 36-39, 53, 56...	181	Advanced

#	Search	Results	Search type
27	from 26 keep 7, 15, 36-37, 40, 53...	146	Advanced

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