Original Research Article

Relative toxicity of benzodiazepines and hypnotics commonly used for self-poisoning: An epidemiological study of fatal toxicity and case fatality

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Abstract

The relative toxicity of anxiolytic and hypnotic drugs commonly used for self-poisoning was assessed using data on suicides, prescriptions and non-fatal self-poisonings in England, 2005–2012. Data on suicide by self-poisoning were obtained from the Office for National Statistics, information on intentional non-fatal self-poisoning was derived from the Multicentre Study of Self-harm in England and data on prescriptions in general practice from the Clinical Practice Research Datalink. We used two indices of relative toxicity: fatal toxicity (the number of fatal self-poisonings relative to the number of individuals prescribed each drug) and case fatality (the number of fatal relative to non-fatal self-poisonings). Diazepam was the reference drug in all analyses. Temazepam was 10 times (95% confidence interval 5.48–18.99) and zopiclone/zolpidem nine times (95% confidence interval 5.01–16.65) more toxic in overdose than diazepam (fatal-toxicity index). Temazepam and zopiclone/zolpidem were 13 (95% confidence interval 6.97–24.41) and 12 (95% confidence interval 6.62–22.17) times more toxic than diazepam, respectively (case-fatality index). Differences in alcohol involvement between the drugs were unlikely to account for the findings. Overdoses of temazepam and zopiclone/zolpidem are considerably more likely to result in death than overdoses of diazepam. Practitioners need to exercise caution when prescribing these drugs, especially for individuals who may be at risk of self-harm, and also consider non-pharmacological options.

Keywords

Minor tranquilisers, sedatives, relative toxicity, suicide, self-harm, self-poisoning

Introduction

Minor tranquilisers (anxiolytics) and hypnotic drugs are used extensively for the treatment of various psychological problems, including anxiety disorders and insomnia (Alessi-Severini et al., 2014). According to data from the National Health Service (NHS) Business Services, over 16 m prescriptions for minor tranquilisers and hypnotics were written and dispensed in England in 2013, benzodiazepines accounting for 58% of these and 'Z-drugs' (i.e. zopiclone, zaleplon and zolpidem) accounting for 39% (National Institute for Health and Care Excellence, 2014). Self-poisoning is a common method of self-harm. Data from the Multicentre Study of Self-harm in England show that 79% of all presentations to emergency departments following self-harm are due to self-poisoning, and 14% of these involve benzodiazepines/hypnotics (Geulayov et al., 2016). Insomnia and psychiatric disorders including anxiety are common in patients who self-harm (Hawton et al., 2013; Hysing et al., 2015; Khan et al., 2002; Perlis et al., 2016) so that many individuals at risk for self-harm are in receipt of these medications.

Data on the relative toxicity of individual benzodiazepines/hypnotic medications are sparse, but some differences in toxicity have been reported within the class of benzodiazepines. Buckley and co-investigators, for example, found that temazepam had a greater sedative effect relative to other benzodiazepines when consumed in overdose (Buckley et al., 1995). Reith et al. reported similar toxic risk for zopiclone to that of benzodiazepines as a

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group (Reith et al., 2003), although their study was very small, including only 12 zopiclone-related deaths. Given the widespread use of anxiolytic and hypnotic medications and their significant involvement in acts of self-poisoning, together with the scarcity of published research in this area, there is a need for further investigation of their relative safety.

In this study we focussed on the anxiolytic and hypnotic drugs diazepam, temazepam, chlordiazepoxide, lorazepam, nitrazepam and zopiclone because they are commonly used for both fatal and non-fatal self-poisoning in the UK. Data from the Office for National Statistics (ONS), for example, show that benzodiazepines and Z-drugs (zopiclone and zolpidem) were involved in 14% of deaths due to self-poisoning (including both suicides and accidental deaths) in England and Wales in 2012 (diazepam and zopiclone/zolpidem accounted for 79% of those; Office for National Statistics, 2014) similar to their involvement in non-fatal hospital presentations for self-poisoning (Geulayov et al., 2016). The benzodiazepines/hypnotics investigated in the present study were also the most widely prescribed in the community in England as highlighted in a report by NHS Digital, 2015.

Our overall aim was to provide information on the relative toxicity of these drugs which may assist clinicians in making decisions about prescribing and contribute to policy advice of regulatory agencies. We used two indices of relative toxicity: (a) fatal toxicity: for each drug we calculated the number of self-poisoning deaths relative to the number of individuals prescribed this drug; (b) case fatality: the number of self-poisoning deaths relative to the number of episodes of non-fatal self-poisoning involving this drug. We also examined the extent of alcohol involvement in fatal self-poisoning as concerns have been raised about the interactions of these drugs with alcohol (Koski et al., 2002).

Methods

In this analysis of data on suicides, prescriptions and non-fatal self-poisonings in England (2005–2012), we investigated the relative toxicity of the following benzodiazepine/sedative medications: diazepam, temazepam, chlordiazepoxide, lorazepam, nitrazepam, zopiclone and zolpidem. The 'Z-drugs' were grouped into a single group of 'zopiclone/zolpidem', in keeping with data from the Clinical Practice Research Datalink (CPRD). Data on prescriptions as provided by CPRD did not differentiate between the Z-drugs because only 1% of the prescriptions were for zolpidem. The remaining were for zopiclone. This led to our decision to merge zopiclone and zolpidem into a single category in all analyses. Data from the ONS and from the Multicentre Study of Self-harm in England, in which 'Z-drugs' are recorded separately, showed that the vast majority of events involving these drugs (86% and 93%, respectively) were due to the ingestion of zopiclone, a figure consistent with data from NHS Digital (2015).

Data used in this study were for the eight complete years 2005–2012. We obtained data separately by gender and by single year of age.

Data sources

Deaths. Information on deaths due to self-poisoning with benzodiazepine/hypnotic medications was provided by ONS based on deaths in England occurring during 2005–2012 which were registered by the end of 2013 (location was assigned using postcode of usual residence based on the November 2013 National Statistics Postcode Directory). Deaths receiving a verdict of intentional self-poisoning or death of undetermined intent (open verdict) that involved the study benzodiazepines/sedative medications were included. Open verdicts were included in accordance with current policy on suicide statistics and research in the UK, on the basis that the majority are possible suicides (Gunnell et al., 2013; Linsley et al., 2001; Office for National Statistics, 2015). Deaths by accidental self-poisoning were excluded. Therefore, the term 'suicide' in this paper includes intentional self-poisoning together with open verdicts.

Non-fatal self-poisoning. Information on non-fatal self-harm by self-poisoning was obtained from the Multicentre Study of Self-harm in England. The study is described in detail elsewhere (Hawton et al., 2007). It involves data collection on all presentations for self-harm to the emergency departments at five general hospitals in Oxford (one hospital), Manchester (three hospitals) and Derby (two hospitals that merged into one in 2009). Self-harm is defined as intentional self-poisoning or self-injury, irrespective of the motivation or degree of suicidal intent (Hawton et al., 2003). Self-poisoning with drugs includes the intentional ingestion of more than the prescribed amount of any drug, whether or not there is evidence that the act was intended to result in death. Data were collected on gender, age, date and method of self-poisoning, including the specific drugs ingested. Data were extracted for all episodes of non-fatal self-poisoning involving individuals aged 15 years and over which included the study benzodiazepine/hypnotic medication, regardless of whether or not other drugs or alcohol were involved. Only episodes by individuals who (at the time of the self-harm episodes) resided in the catchment area of Oxford City, Manchester City and the Derby Unitary area were included in the analysis because reliable mid-year population estimates, which are required to calculate rates, were available for these areas.

Prescription of medications. Data on benzodiazepine/hypnotic medications dispensed in the community in England were obtained from the CPRD (The Clinical Practice Research Datalink (CPRD), 2016). The CPRD is a governmental research service which provides anonymised primary care records for research. It currently contains data on approximately 7% of the UK population. Information from the CPRD included the number of patients registered with the general practices appearing in the CPRD database and the number of individuals who were prescribed a specific study medication, by year (2005–2012), age and gender.

Measures of toxicity

We used two indices of relative toxicity.

Fatal toxicity. For each benzodiazepine/sedative drug we calculated the number of deaths by self-poisoning in England during 2005–2012 attributed to this drug divided by the number of individuals prescribed this drug during the equivalent period and standardised these to the risk for diazepam to derive the fatal-toxicity index.

Case fatality. The number of deaths by self-poisoning in England during 2005–2012 attributed to a given drug divided by the number of episodes of non-fatal self-poisoning involving this drug during the equivalent period from the Multicentre Study of Self-harm in England and standardised these to the risk for diazepam to derive the case-fatality index.

Diazepam was chosen as the reference drug because it is the most widely prescribed benzodiazepine in the UK (The Clinical Practice Research Datalink (CPRD), 2016) and is most commonly used for self-poisoning (Camidge et al., 2003).

Alcohol involvement

Information on the presence of alcohol in cases of fatal self-poisoning was obtained from ONS records and was based on the coroners' toxicology reports.

Ethical approval

The monitoring systems for self-harm in Oxford and Derby have approval from local Health/Psychiatric Research Ethics Committees to collect data on self-harm for local and multicentre projects. Self-harm monitoring in Manchester is part of a clinical audit system, and has been ratified by the local Research Ethics Committee. All three monitoring systems are fully compliant with the Data Protection Act (1998). All centres have approval under Section 251 of the NHS Act (2006) to collect patient identifiable information without explicit patient consent.

We obtained specific Independent Scientific Advisory Committee (ISAC) approval from the CPRD (protocol number 14_064R2) and from ONS to obtain prescriptions and mortality data, respectively.

Statistical analysis

We calculated rates of suicide by self-poisoning per 100,000 person-years using England's mid-year population estimates for 2005–2012 obtained from ONS (Office for National Statistics, 2016). Rates of non-fatal self-poisoning were based on the number of episodes of non-fatal self-poisoning per 100,000 person-years using mid-year population estimates obtained from the Office for National Statistics, 2016, for 2005–2012 for the geographical areas covered by the Multicentre Study of Self-harm (Oxford City, the City of Manchester and Derby Unitary area). Prescription rates were calculated as the number of individuals prescribed a specific medication per 100,000 person-years registered with the general practices in the CPRD during 2005–2012. The analyses were carried out using the Poisson distribution with exact 95% confidence intervals (CIs).

Relative toxicity of specific drugs was calculated by computing ratios of the number of deaths involving each drug to the total number of individuals prescribed the specific drugs (fatal toxicity) or to the total number of episodes of non-fatal self-poisoning with each drug (case fatality). Confidence intervals for relative toxicity were calculated using the Poisson distribution.

We conducted two sets of analyses for each of the toxicity indices used in this study (fatal toxicity and case fatality). First, we included only deaths involving single drugs (with or without alcohol). Second, we also included cases of suicides involving multiple drugs where the drug of interest was the first drug recorded by the coroner. We did this on the basis that the first-recorded drug was likely to be the main cause of death.

In a further analysis we differentiated between zopiclone and zolpidem and calculated separate case-fatality index (suicide to non-fatal self-poisoning). This was possible because data on suicides and non-fata self-poisoning were recorded separately for zopiclone and zolpidem.

We ran the analyses by gender and examined the proportion of alcohol involvement in fatal self-poisoning in each of the medications studied. Analysis by age was not possible due to small numbers.

Statistical analysis was carried out using Stata 14.1.

Results

Fatal toxicity

During 2005–2012, there were 179 suicides (~22 suicides per year) due to self-poisoning involving a benzodiazepine/hypnotic drug where the benzodiazepine/hypnotic drug was the only self-poisoning agent. There were an additional 109 suicide deaths (~14 per year) where the benzodiazepine/hypnotic was consumed with other medications but was listed as the first self-poisoning agent (i.e. 288 in total). During this period approximately 5% of individuals aged 15 years and over included in the CPRD were prescribed at least one of the study benzodiazepines/hypnotics annually.

The prescription data showed that diazepam was the most prescribed benzodiazepine/hypnotic, followed by zopiclone/zolpidem, while chlordiazepoxide was the least prescribed medication of the drugs under investigation (Table 1). The highest numbers of suicide deaths during the study period were recorded for zopiclone/zolpidem, followed by temazepam, while lorazepam was implicated in the fewest deaths (Table 1).

Findings for the relative toxicity of the individual benzodiazepine/hypnotic drugs as measured by the fatal-toxicity index (suicide deaths relative to individuals prescribed each drug) where the drug under investigation was the only self-poisoning agent recorded (Table 2) showed that temazepam was the most toxic drug i.e. over 10-fold times more toxic than the reference drug, diazepam (odds ratio (OR) 10.20, 95% CI 5.48–18.99). Similarly, zopiclone/zolpidem were over nine times more toxic than diazepam (OR 9.14, 95% CI 5.01–16.65). Nitrazepam and chlordiazepoxide were over six times more toxic than diazepam (OR 6.65, 95% CI 2.14–20.62; OR 6.28, 95% CI 2.47–15.96, respectively). While the relative toxicity indices for temazepam, chlordiazepoxide and nitrazepam were higher for females than for males, the overlap between CIs suggest weak evidence for gender differences (this was not formally tested).

In a second set of analyses we estimated fatal toxicity including also deaths in which the drug under investigation appeared with other medication but was listed as the first drug (Table 2). The findings appeared smaller in magnitude, showing that temazepam and zopiclone/zolpidem were approximately five times more toxic than diazepam while nitrazepam was almost three times more toxic than diazepam, but the evidence for greater toxicity of chlordiazepoxide was weak. It is worth noting that the majority of fatal poisonings involving temazepam (72%), chlordiazepoxide (100%), nitrazepam (78%) and zopiclone (62%)

Table 1. The number and rates of suicides involving single drugs or single and multiple (first-listed) drugs in England and the number and rate of individuals prescribed each of the medications (from the Clinical Practice Research Datalink), in individuals aged 15 years and over, 2005–2012.

	Fatal self-poisoning in England (2005–2012)				Prescriptions (2005–2012)	
	Single drug		Single drug and first drug listed			
	Total *n*	Death rate per 100,000 person-years (95% CI)	Total *n*	Death rate per 100,000 person-years (95% CI)	Average number per year	Prescription rate per 100,000 person-years (95% CI)
Diazepam	12	0.0035 (0.0018–0.0061)	35	0.0102 (0.0071–0.0142)	89,930	1946.08 (1941.59–1950.59)
Temazepam	58	0.0170 (0.0129–0.0219)	81	0.0236 (0.0188–0.0294)	42,629	922.49 (919.40–925.59)
Chlordiazepoxide	4	0.0012 (0.0003–0.0030)	4	0.0012 (0.0003–0.0030)	4508	97.56 (96.55–98.57)
Lorazepam	2	0.0006 (0.00007–0.0021)	5	0.0015 (0.0005–0.0034)	10,678	231.06 (229.52–232.62)
Nitrazepam	7	0.0021 (0.0008–0.0004)	9	0.0026 (0.0012–0.0050)	8351	180.72 (179.36–182.10)
Zopiclone/ zolpidem	96	0.0281 (0.0227–0.0343)	154	0.0450 (0.0382–0.0527)	78,750	1704.17 (1699.96–1708.38)
All drugs	179		288		234,846	

CI: confidence interval.

Table 2. Fatal-toxicity index – the number of suicides involving a given drug per individuals prescribed this drug relative to diazepam: single-drug only and single or first-listed drug, by gender.

	Odds ratio (95% CI)		
	Both genders	Males	Females
Single drug suicides only			
Diazepam	Reference	Reference	Reference
Temazepam	10.20 (5.48–18.99)	7.81 (3.39–17.99)	13.53 (5.27–34.71)
Chlordiazepoxide	6.65 (2.14–20.62)	3.78 (0.79–18.19)	10.89 (2.11–56.13)
Lorazepam	1.40 (0.31–6.27)	1.17 (0.14–9.53)	1.71 (0.20–14.62)
Nitrazepam	6.28 (2.47–15.96)	3.55 (0.74–17.09)	10.06 (2.91–34.76)
Zopiclone/zolpidem	9.14 (5.01–16.65)	9.71 (4.45–21.18)	7.61 (2.97–19.53)
Single drug and first listed drug suicides			
Diazepam	Reference	Reference	Reference
Temazepam	4.88 (3.28–7.26)	3.20 (1.89–5.42)	8.10 (4.29–15.29)
Chlordiazepoxide	2.28 (0.81–6.42)	1.15 (0.27–4.88)	4.54 (1.02–20.28)
Lorazepam	1.20 (0.47–3.07)	0.36 (0.05–2.64)	2.85 (0.92–8.83)
Nitrazepam	2.77 (1.33–5.76)	1.62 (0.49–5.40)	5.03 (1.89–13.41)
Zopiclone/zolpidem	5.03 (3.48–7.25)	4.80 (3.06–7.54)	4.96 (2.63–9.30)

CI: confidence interval.

were reported as single drug self-poisonings, while this was the case for 34% and 40% of fatal self-poisonings involving diazepam and lorazepam, respectively.

Case fatality

During 2005–2012 there were on average 576 non-fatal self-poisoning presentations a year involving benzodiazepine/sedative drugs to the emergency departments in the general hospitals in the three centres participating in the Multicentre Study of Self-harm in England by individuals residing in the catchment areas of the three study sites (Table 3). Diazepam was the most commonly used drug in these episodes, followed by zopiclone/zolpidem, while nitrazepam was the least commonly used of the drugs under investigation.

Consistent with our findings from the fatal-toxicity analysis, using the case-fatality index (suicide deaths to non-fatal self-poisoning episodes) the relative toxicity of individual drugs where the drug under investigation was the only agent recorded in the fatal poisonings showed that temazepam and zopiclone/zolpidem were 13- and 12-fold more toxic than the reference drug diazepam, respectively (OR 13.04, 95% CI 6.97–24.41; OR 12.12, 95% CI 6.62–22.17, respectively) (Table 4). Furthermore, the relative toxicity estimates were markedly larger for nitrazepam and chlordiazepoxide relative to diazepam (OR 6.28, 95% CI 2.44–16.14; OR 3.27, 95% CI 1.05–10.24, respectively), while the toxicity of lorazepam was comparable to that of diazepam. There was some indication that the toxicity of all the drugs other than zopiclone/zolpidem may be greater in females than males, although this was not formally tested.

Table 3. The number and rate of suicides involving single-drugs or single and multiple (first-listed) drugs in England and the number and rates of non-fatal self-poisoning episodes in three centres in England, in individuals aged 15 years and over (2005–2012).

	Fatal self-poisoning in England (2005–2012)				Non-fatal self-poisoning in the three centres (2005–2012)	
	Single drug		Single drug and first listed drug			
	Total *n*	Death rate per 100,000 person-years (95% CI)	Total *n*	Death rate per 100,000 person-years (95% CI)	Average number per year	Prescription rate per 100,000 person-years (95% CI)
Diazepam	12	0.0035 (0.0018–0.0061)	35	0.0102 (0.0071–0.0142)	250	34.92 (33.41–36.48)
Temazepam	58	0.0170 (0.0129–0.0219)	81	0.0236 (0.0188–0.0294)	93	12.94 (12.03–13.91)
Chlordiazepoxide	4	0.0012 (0.0003–0.0030)	4	0.0012 (0.0003–0.0030)	26	3.56 (3.09–4.08)
Lorazepam	2	0.0006 (0.00007–0.0021)	5	0.0015 (0.0005–0.0034)	30	4.19 (3.67–4.75)
Nitrazepam	7	0.0021 (0.0008–0.0004)	9	0.0026 (0.0012–0.0050)	23	3.24 (2.79–3.75)
Zopiclone/zolpidem	96	0.0281 (0.0227–0.0343)	154	0.0450 (0.0382–0.0527)	165	23.06 (21.83–24.34)
All drugs	179		288		576	

CI: confidence interval.

Table 4. Case fatality – the number of suicides involving a given drug per non-fatal self-poisoning episodes relative to diazepam: single-drug only and single or first-listed drug, by gender.

	Odds ratio (95% CI)		
	Both genders	Males	Females
Single drug suicides only			
Diazepam	Reference	Reference	Reference
Temazepam	13.04 (6.97–24.41)	10.50 (4.51–24.44)	16.73 (6.48–43.20)
Chlordiazepoxide	3.27 (1.05–10.24)	2.16 (0.44–10.52)	4.98 (0.95–26.03)
Lorazepam	1.39 (0.31–6.25)	1.41 (0.17–11.63)	1.50 (0.17–12.93)
Nitrazepam	6.28 (2.44–16.14)	3.01 (0.61–14.71)	10.94 (3.11–38.40)
Zopiclone/zolpidem	12.12 (6.62–22.17)	14.93 (6.79–32.82)	9.22 (3.58–23.76)
Single drug and first-listed drug suicides			
Diazepam	Reference	Reference	Reference
Temazepam	6.24 (4.16–9.37)	4.30 (2.50–7.40)	10.02 (5.29–19.09)
Chlordiazepoxide	1.12 (0.40–3.19)	0.66 (0.15–2.85)	2.08 (0.46–9.41)
Lorazepam	1.19 (0.46–3.07)	0.43 (0.06–3.23)	2.50 (0.80–7.85)
Nitrazepam	2.77 (1.31–5.85)	1.37 (0.40–4.67)	5.47 (2.01–14.87)
Zopiclone/zolpidem	6.67 (4.59–9.68)	7.38 (4.64–11.75)	6.00 (3.18–11.34)

CI: confidence interval.

There were similar findings when fatal toxicity was calculated by including single and first-drug listed suicides (Table 4), although the effect estimates were markedly smaller. Nitrazepam was almost three times more toxic than diazepam but there was weak evidence for greater toxicity of chlordiazepoxide in this analysis.

A direct comparison between temazepam and zopiclone/zolpidem showed no evidence of a difference between the two hypnotic drugs. This finding was consistent across indices of relative toxicity and in the analysis using single as well as poly-drug self-poisoning (results not shown).

In a further analysis we separated zolpidem and zopiclone fatal and non-fatal self-poisonings. Using the single drug suicides only, the analysis showed that ingesting zolpidem was 20.6 times more likely to result in death relative to diazepam (OR 20.6, 95% CI 8.86–48.01) while ingesting zopiclone was 11.5 times more likely to result in death than diazepam (OR 11.50, 95% CI 6.23–21.14). A direct comparison between zolpidem and zopiclone indicated that zolpidem was 1.8 more likely to result in death relative to zopiclone but this was consistent with chance (OR 1.80, 95% CI 0.92–3.48). The inclusion of multiple drug fatal self-poisonings showed that zolpidem was 13.5 times more toxic than diazepam (OR 13.50, 95% CI 7.55–24.16) while zopiclone was 6.2 times more toxic than diazepam (OR 6.17, 95% CI 4.22–9.01). A direct comparison between zolpidem and zopiclone indicated that zolpidem was 2.2 times more likely to result in death relative to zopiclone (OR 2.19, 95% CI 1.32–3.64) (results are not shown in tables).

Alcohol involvement

There were some variations in the proportion of individuals for whom alcohol was reported by coroners as being present in their

blood after death by self-poisoning. Focussing on the drugs involved in at least 10 single-drug deaths, this was 20.7% (12/58) for temazepam, 33.3% (4/12) for diazepam and 37.6% (36/96) for zopiclone/zolpidem. For deaths involving single or multiple drugs (where the drug of interest was the first-listed drug), the proportion of individuals for whom the presence of alcohol was recorded was very similar to those found for single-drug deaths.

Discussion

We have investigated the relative toxicity of benzodiazepine and hypnotic drugs commonly used for self-poisoning. Using two methods to calculate relative toxicity of individual benzodiazepine/hypnotic medications, there was consistent evidence that overdoses of temezepam and zopiclone/zolpidem were considerably more likely to result in death than overdoses of diazepam. A more inclusive approach, including deaths involving single and multiple drugs, led to the same conclusion. Chlordiazepoxide and nitrazepam were approximately six times more toxic than diazepam but inclusion of multiple-drug suicides attenuated these differences, although nitrazepam remained somewhat more toxic than diazepam. Temazepam, chlordiazepoxide and nitrazepam appeared to be more toxic in females than males, although no formal gender comparisons were conducted due to small numbers.

The increased risk of fatal self-poisoning attributed to temazepam and zopiclone/zolpidem, and to a lesser extent nitrazepam, may suggest that these medications are inherently more toxic than other minor tranquilisers/hypnotics and therefore lead to more deaths when taken in overdose. Alternatively, differences between the patient groups prescribed these drugs may account for the observed differences. For example, individuals who suffer from insomnia (and who are mostly treated pharmacologically with zopiclone/zolpidem or temazepam) are also at a greater risk of death by suicide (Bjorngaard et al., 2011; Hysing et al., 2015; Perlis et al., 2016). Similarly, chlordiapoxide, is often prescribed for the management of withdrawal symptoms in alcohol dependence, although chlordiapoxide was among the least toxic drugs in this analysis. Furthermore, there may be differences in therapeutic doses required to treat insomnia and those required to alleviate symptoms of anxiety (by e.g. diazepam, lorazepam) which may, in turn, lead to a difference in access to a potentially lethal dose – a risk factor for completed suicide (Hawton, 2007). Other factors which may have contributed to the observed differences in lethality may have been related to differences in the dose ingested and to the co-ingestion of alcohol or other substances (see limitations below).

Buckley and colleagues (Buckley et al., 1995) also showed heightened toxicity, as indexed by greater sedation, for temazepam in overdose relative to other benzodiazepines in patients who self-poisoned, independently of age, gender, dose ingested and co-ingestion of alcohol. The authors, however, did not investigate fatal poisoning and did not include zopiclone or zolpidem in their analysis. Similarly, temazepam was found to have the second highest fatal-toxicity index (including suicides and deaths by accidental self-poisoning), after flurazepam, among hypnotic and anxiolytic medications examined in a UK-based study (Serfaty and Masterton, 1993). This finding is in keeping with that of Buckley and McManus's study in which temazepam was ranked third highest among other sedatives/hypnotics evaluated in terms of deaths per number of prescriptions, although zopiclone and zolpidem were ranked among the least toxic in this study and even less toxic relative to diazepam (Buckley and McManus, 2004). Nevertheless, in a Norwegian study the investigators compared the risk of fatal and non-fatal acute poisoning, including suicides and accidental deaths, associated with zopiclone and benzodiazepines. Their findings showed that zopiclone was approximately four times more toxic than other benzodiazepines (Bjornaas et al., 2010). However, benzodiazepines were analysed as a single group, precluding direct comparison with our results. Furthermore, a review by the World Health Organization (WHO) has highlighted the frequent involvement of sedative hypnotics including nitrazepam and zopiclone in suicides by self-poisoning (World Health Organization (WHO), 2006).

Some pharmacological properties of diazepam, temazepam and zopiclone should also be considered. These drugs are rapidly absorbed so that a differential onset of action for pharmacokinetic does not seem a likely explanation. As noted above, temazepam seems to produce more sedation in overdose than other benzodiazepines (Buckley et al., 1995), and in animal studies both the affinity of temazepam for central benzodiazepine receptors and its speed of occupation were greater than in diazepam (Muller and Stillbauer, 1983). Despite this, clinical conversion tables often suggest that temazepam is less potent than diazepam (Alexander and Perry, 1991), which raises the possibility that, in clinical use, temazepam is dosed relatively more heavily than diazepam. Another factor that might be relevant is that diazepam, unlike zopiclone and temazepam, is metabolised to a long-acting metabolite desmethyldiazepam. In animal studies, desmethyldiazepam has lesser potency than diazepam at the central benzodiazepine receptor and, indeed, has been suggested to act as a partial agonist at this site (Gobbi et al., 1987). This raises the possibility that, during overdose, conversion of diazepam to the less potent desmethyldiazepam might be relatively protective against the toxicity of the parent compound.

Both temazepam and zopiclone have been popular as hypnotic agents because their relatively short duration of action is believed to lessen the extent of daytime 'hangover' effects. Data from the CPRD show that zopiclone is the second, and temazepam the third, most commonly prescribed of the study drugs after diazepam. Also, prescribing of 'Z-drugs' in England has increased in recent years (NHS Digital, 2016). Our finding that zopiclone/zolpidem and temazepam when taken in overdose are associated with a markedly greater risk of death than the other study drugs, coupled with the finding that individuals who suffer from insomnia are at a greater risk of self-harm and suicide (Bjorngaard et al., 2011; Hysing et al., 2015; Perlis et al., 2016), highlights both a) the need for further evaluation of the safety profile for these drugs and b) the importance of increasing the availability of non-pharmacological treatments. The latter include interventions such as advice on good sleep hygiene as well as cognitive behavioural therapy (CBT) (Siebern et al., 2012) which have been shown to be effective, and even superior to medications, in managing insomnia, especially in the long-term (Mitchell et al., 2012). Use of CBT as a first-line treatment for insomnia was included in the National Institute for Health and Care Excellence (NICE) guidance to the NHS over a decade ago (National Institute for Health and Care Excellence, 2004). It was further concluded that there had been no compelling evidence of a difference between the Z-drugs and short-acting benzodiazepines in terms

of effectiveness, adverse effects, or potential for misuse or dependence (Gibson, 2004; National Institute for Health and Care Excellence, 2004), although the fact that short-acting benzodiazepines are associated with next-day residual effects cannot be overlooked.

Strengths and weaknesses

Major strengths of this study are the large sample size, the inclusion of eight years of data and the use of two approaches to assessing toxicity that both converge on the same conclusion. However, some limitations should be considered. The data sources in this investigation are not linked, so the indices are based on largely different populations. Information on prescriptions of medications were obtained from the CPRD which includes data on approximately 7% of the population actively registered with one of 674 participating practices across the UK although CPRD patients are broadly representative of the UK population in terms of age, sex and ethnicity (Herrett et al., 2015). Another potential source of prescribing data would be national sources such as NHS sources on prescribing (https://digital.nhs.uk/catalogue/PUB23631). However, these data are for overall numbers of prescriptions rather than individuals and are not provided by gender. Crude comparisons of findings for fatal toxicity based on these national data indicate that they would be similar to the findings in our study, with particularly high toxicity indices of temazepam and the Z-drugs. Information on non-fatal self-poisonings in the present study was based on the Multicentre Study of Self-harm in England, which involves all presentations to five general hospitals in Oxford, Manchester and Derby. These three centres include a socioeconomically diverse population. On the basis of the Index of Multiple Deprivation, 2007, for England (Department for Communities and Local Government, 2008), which combines information from several domains including income, employment, education, skills and training, health and disability, crime, barriers to housing and services, and living environment, Manchester was ranked the fourth most deprived local authority in England, Derby was ranked 69th and Oxford 155th. Additionally, the consistency in findings using the fatal-toxicity and the case-fatality approaches increases confidence in the results.

Furthermore, we were unable to distinguish between the different 'Z-drugs' in our analyses of fatal toxicity as 'Z-drugs' in the CPRD (prescriptions) data were merged into a single category of zopiclone/zolpidem, although we were able to calculate case fatality separately for zopiclone and zolpidem since data from ONS and from the Multicentre Study of Self-harm differentiated between these drugs.

Our primary analyses are based on single-agent indices of toxicity. Although this method can provide greater certainty about the agent which caused death, multiple drugs are involved in many cases. We have carried out further analyses of multiple drugs used in fatal self-poisoning, the results of which were in keeping with the results of the primary analysis. Notably, the majority of fatal poisonings involving the drugs deemed more toxic in this study were single drug self-poisoning deaths: temazepam (72%), nitrazepam (78%) and zopiclone/zolpidem (62%), compared to 34% and 40% of deaths involving diazepam and lorazepam, respectively. We did not account for the amount of medication consumed in overdose as data provided by the ONS do not include this information. Another question is whether fatal self-poisoning is related to greater involvement of alcohol or of other medications. Concerns have been raised about the safety of benzodiazepines/hypnotics in combination with alcohol, which may lead to respiratory failure (Koski et al., 2002). Our examination of alcohol involvement in fatal self-poisoning suggests that there might be some differences in the proportion of alcohol involvement in the different drugs, but these differences are not likely to account for the observed findings. For example, the proportion of individuals who had alcohol reported in combination with temazepam was lower than the proportion of individuals who had alcohol reported in combination with diazepam while the proportion of individuals who had alcohol reported in combination with zopiclone/zolpidem was slightly higher than that reported for diazepam. However, data on alcohol involvement in suicide deaths may be incomplete as the accuracy of Coroner's reports on presence of alcohol is uncertain. Nevertheless, in toxicological examination of 204 persons who died by suicide in the US, alcohol was recorded in 35% of toxicology reports for individuals who tested positive for hypnotics (Mendelson and Rich, 1993), although this study might also have been subjected to under-recording of alcohol involvement.

A further point which merits discussion is the inclusion of open verdicts as suicides. As stated above, we included deaths by self-poisonings which received a suicide or open verdict codes by the coroners, in accordance with current policy on suicide statistics and research in the UK (Office for National Statistics, 2015). The proportions of individuals whose deaths received an open verdict were 33.9% (single drug deaths) and 37.4% (single or multiple drugs deaths). Previous research suggest some inconsistencies between research-defined and coroner defined open verdict classifications as suicides, although temporal and area variations have also been reported (Gunnell et al., 2013; Linsley et al., 2001). This may be a limitation of the present data although we have no reason to believe that the level of misclassification is different between the drugs under investigation.

Lastly, the extent to which individuals who self-poisoned with zopiclone/zolpidem and temazepam had used medication prescribed for them or drugs obtained through other means is unclear. It has been reported, for example, that people who obtain zopiclone through unregulated sources tend to consume larger quantities of the drugs and in combination with other substances than those using prescribed medication (Newcombe, 2009).

Conclusion and policy implications

The CPRD data indicate that during 2005–2012, approximately 250,000 individuals were prescribed the study benzodiazepines/hypnotics by a general practitioner each year. Extrapolating to the population of England, this is equivalent to approximately 2.5m individuals aged 15 years and over each year.

Earlier concerns about the health risks associated with prolonged use of benzodiazepines/hypnotic drugs (Weich et al., 2014) stimulated legislative changes to prescription-writing requirements in the UK (British National Formulary, 2014; British National Formulary, 2017), and also storage and recording requirements in Australia (The Goverment of Western Australia - Department of Health, 2013). However, the findings of the present investigation, together with those of other studies highlighted above, suggest that temazepam and zopiclone/zolpidem may be associated with a substantially greater risk of death

in persons who self-poison. Therefore, policymakers and practitioners may need to consider the apparent differential risks of these drugs, especially as they are the two most commonly prescribed hypnotics (at least in the UK). Furthermore, given the potential impairment in functioning and distress associated with insomnia and in the absence of safer drug alternatives, there is a need for greater focus on psychological management of sleeping problems, especially when dealing with vulnerable patients. Further studies which include reliable recording of multiple-drug involvement and alcohol in fatal and non-fatal self-poisoning as well as information about doses ingested are required in order to confirm our findings.

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