Antihistamine-related deaths in England: Are the high safety profiles of antihistamines leading to their unsafe use?

Princess J. Oyekan | Hayley C. Gorton | Caroline S. Copeland

Institute of Pharmaceutical Sciences, King’s College London, London, UK
Department of Pharmacy, School of Applied Sciences, University of Huddersfield, Huddersfield, UK
Population Health Research Institute, St George’s, University of London, London, UK

Correspondence
Caroline S. Copeland, Lecturer in Pharmaceutical Medicine; Institute of Pharmaceutical Sciences King’s College London Franklin Wilkins Building 5th Floor Stamford Street, London SE1 9NH, UK.
Email: caroline.copeland@kcl.ac.uk

Aims: Antihistamines are routinely taken to control allergic reactions or sedation to induce sleep. There are, however, growing concerns regarding sedating antihistamine misuse. This research aims to evaluate deaths related to antihistamines in England occurring during 2000–2019.

Methods: Cases reported to the National Programme on Substance Abuse Deaths from England occurring in 2000–2019 with antihistamine detections at postmortem were extracted for analysis.

Results: In total, 1666 antihistamine postmortem detections were identified from 1537 cases. Sedating antihistamines available for purchase under pharmacist supervision but without need for a prescription (pharmacy-only medications) were present in a significant majority of cases (85.2%, P < .01). Despite an increasing trend for antihistamine-related deaths over time, the proportion of deaths where an antihistamine was implicated declined over the same period. Specific concerns with regards to the misuse of these pharmacy-only sedating antihistamines are raised with regards to the significant proportion of cases that were concluded as suicide (20.9%, P < .01), and the high prevalence of their use in combination with other central nervous system depressants (94.8% of cases).

Conclusion: This is the first report in over 40 years regarding antihistamine-related mortality from England. The rising trend in sedating antihistamine-related deaths may be contributed to by their increasing availability and the perceived negligible dangers associated with antihistamines, both from the general public and learned professionals. Awareness of the dangerous sedative properties that some antihistamines possess is, however, heightened in individuals deliberately seeking these effects. Urgent review of sedating antihistamines currently assigned under the pharmacy-only classification is needed to achieve antihistamine harm reduction.

Keywords: antihistamine, drug-related death, England, polypharmacy, postmortem, substance misuse

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2021 The Authors, British Journal of Clinical Pharmacology published by John Wiley & Sons Ltd on behalf of British Pharmacological Society.
INTRODUCTION

Histamine is an endogenous compound most commonly associated with the inflammatory response elicited by allergic reactions. However, histamine possesses multitudinal physiological roles throughout the human body, including as a neurotransmitter in the central nervous system (CNS) where it is involved in regulation of the sleep-wake cycle and arousal. Antihistamine medications have been designed and licensed that specifically target peripheral histamine receptors responsible for mediating allergic reactions, or histamine receptors in the CNS responsible for mediating wakefulness. As such, antihistamines are broadly categorised by the location of the histamine receptors upon which they are able to act: first-generation antihistamines freely cross the blood–brain barrier and enter the CNS where they elicit sedative properties; second-generation antihistamines do not readily cross the blood–brain barrier and therefore do not cause sedation, targeting only peripheral histamine receptors. Second-generation antihistamines are thus often marketed as non-drowsy medications, aimed at individuals seeking only to control allergic responses.

The UK Medicines Act defines the 3 main categories by which medicines can be legally obtained in the UK: prescription-only medicines (POM) can only be supplied against a prescription or direction from a valid practitioner; pharmacy medicines (P) can be purchased from a pharmacy under the supervision of a pharmacist; and general sales list (GSL) medicines can be bought from any retail outlet. Both P and GSL medications are classified as over-the-counter (OTC) medications. Antihistamines are commonly used medicines and, in many countries including the UK, are available OTC without prescription. OTC status is indicative of a favourable safety vs. benefit profile. However, there are emerging concerns regarding antihistamine misuse potential, especially first-generation sedating compounds available without prescription.

Worldwide, antihistamines have been implicated in both accidental and intentional deaths. In the USA, diphenhydramine is 1 of the 10 most commonly implicated medications in overdose deaths, equating to over 2000 (3%) of all drug overdose deaths. It is also the third most common medicine involved in suicides that involved a single drug. Furthermore, antihistamines were recorded in 6% of the 1.7 million self-poisoning reports (attempted suicide and suicide) made to the US National Poison Data System between 2010 and 2018. In South Korea, chlorphenamine was the most detected medication in postmortem blood in 2014, and doxylamine was the most common cause of poisoning requiring hospitalisation in 2003. Between 2003 and 2011, the proportion of overall poisonings which included OTC medicines reduced, but the proportion of poisonings involving antihistamines increased from 2 to 10%. In Sweden, alimemazine (trimeprazine) is 1 of the 10 most commonly detected drugs when someone has died by poisoning or hanging; and the 12th most common in deaths of people who have been dependent on drugs. In Australia, doxylamine was implicated in a quarter of deaths involving co-codamol; and in Japan a combination product involving promethazine was the fifth most common drug resulting in intensive care admission following intentional self-poisoning. Diphenhydramine has been shown to exacerbate hepatotoxicity caused by paracetamol when used in combination, and was the most commonly noncontrolled drug concomitantly present in accidental methadone overdose in the USA.

The Office for National Statistics do not include data for antihistamines in the analysis they provide by medication group in their statistical bulletins on deaths related to drug poisoning in England and Wales, and commentary on antihistamine-related mortalities in the UK, to our knowledge, have not been examined for over 40 years. Deaths involving antihistamines, specifically those with sedating properties that are available over the counter in England, are on the rise. However, the perceived contribution of antihistamines in causing death has reduced over the same period.

The over-the-counter availability of sedating antihistamines in England needs urgent review.

METHODS

2.1 NPSAD

NPSAD regularly receives information from coroners on a voluntary basis on deaths related to drugs. If a death has an unknown cause, is violent or unnatural, sudden and unexplained, occurred during an operation or before the person came out of an anaesthetic, or may
have been caused by an industrial disease or poisoning, then it is referred to a coroner.\textsuperscript{20} Toxicology tests are requested at the discretion of the coroner, medical examiner or pathologist, dependent upon the circumstances of individual cases. Coroners report a death to NPSAD if it features 1 or more of the following:

(i) Presence of 1 or more psychoactive substance(s) directly implicated in death;
(ii) History of dependence or abuse of drugs;
(iii) Presence of controlled drugs at postmortem.

The Central Office for Research Ethics Committees (COREC), of the National Patient Safety Agency confirmed (February 2006) that NPSAD does not require NHS Research Ethics Committee review as the subjects of the research are deceased. Neither the General Data Protection Regulation (GDPR) nor the Data Protection Act apply to identifiable data that relate to a person once they have died.

2.2 | Case identification

A range of documents are contained in coronial inquest files, although this varies from case to case. Typically, the coroner has access to: statements from witnesses, family and friends; General Practitioner records (if the deceased is registered with 1); reports from first responders (e.g. police, emergency services); hospital emergency departments and clinical ward reports; psychiatric and substance abuse team reports; and postmortem and toxicology reports.

A retrospective study design was employed to identify relevant cases from England associated with the use of antihistamines by searching the NPSAD database using the “antihistamine” term and variations thereof (e.g. anti histamine; anti-histamine). The fields searched on the database were those holding data on drugs present at postmortem.

All cases reported here have confirmatory evidence from toxicology reports indicating the presence of antihistamine(s) in the sampled decedents’ postmortem tissue(s), demonstrating that the decedent died following recent ingestion of an antihistamine. Antihistamines are tested for using a variety of mass spectrometry and high-pressure liquid chromatography methods, where they are identified by comparison against a routinely-updated library of known antihistamine compounds.\textsuperscript{21,22} Implication in death indicates that the detected antihistamine was identified as a cause of death by the coroner and/or pathologist following conclusion of their comprehensive investigations.

2.3 | Data analysis

Data analysis and statistical tests (Student t test; $\chi^2$) were performed using IBM SPSS Statistics for Windows version 25. Categorisation of antihistamines found at postmortem as having been prescribed, hospital administered, illicitly obtained or unknown in source were delineated based upon information provided in the NPSAD case reports. Prescribing data for antihistamines in England were extracted from OpenPrescribing.net.\textsuperscript{23}

2.4 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries i. http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.\textsuperscript{61}

3 | RESULTS

A total of 1666 antihistamine detections at postmortem were identified from 1537 cases reported to NPSAD from England as of 1 September 2020, covering deaths occurring during the 20-year period from 2000 to 2019.

3.1 | Trends in antihistamine-related deaths and their implication

It is evident that there has been an increase in the reporting of antihistamine-related cases to NPSAD from England (Figure 1A). P antihistamines were present in a significant majority of cases (over 74.8% each year, $P < .01$), with deaths where POM antihistamines were detected representing fewer than 11.9% of cases each year (Figure 1A). Sub-analysis reveals that whilst in a large proportion of these cases the POM antihistamine was illicitly sourced (61.5%; $n = 72/117$), both total number of deaths with a POM antihistamine detected and the proportion of which were illicitly sourced have fallen in recent years (Figure 1B). This is contrary to the POM antihistamine prescribing trend in England over the same period\textsuperscript{23} (Figure 1B). Despite the numerical increase in reported antihistamine-related deaths, there has been a decrease in the implication rate of antihistamines (Figure 2). The lowest implication rate was observed in 2018 (24.3%), yet this was the year with the highest number of cases reported at time of writing (Figure 1A).

3.2 | Types of antihistamines detected

Seventeen different antihistamines were identified in the submitted toxicology reports, with first-generation sedating antihistamines predominating (Table 1). Whilst the proportion of deaths where the first-generation antihistamines cyclizine, diphenhydramine and chlorpheniramine were detected have all significantly increased over the study period (all $P < .05$), the greatest increase is in deaths related to the first-generation antihistamine promethazine ($P < .01$, Figure 3). These first-generation antihistamines were also those with the highest implication rates (diphenhydramine 46.7% of cases, $n = 192/411$;
cyclozine 38.3% of cases, \( n = 153/400 \) of cases; promethazine 34.4% of cases, \( n = 143/416 \); chlorpheniramine 26.4% of cases, \( n = 46/174 \). Comparatively, second-generation antihistamines were significantly less likely to be implicated in causing death (e.g. cetirizine 9.9% of cases, \( n = 10/101 \); loratadine 0.0% of cases, \( n = 0/25 \); both \( P < .01 \)).

### 3.3 | Cause and manner of death

Death was deemed unintentional in 66.1% of cases (\( n = 1016 \)), suicide in 20.9% of cases (\( n = 321 \)) and unclassified in 10.6% of cases (\( n = 162 \)).

Acute drug use was overwhelmingly the most common underlying cause of unintentional deaths (94.1% of cases; \( n = 956/1016 \)). In a further 1.8% of unintentional deaths (\( n = 18/1016 \)) underlying cause of death due to environmental factors (e.g. drowning, fall from a height, road traffic collision) was attributed by the coroner and/or pathologist to reduced levels of consciousness due to acute drug use.

The proportion of antihistamine-related deaths concluded as suicide is significantly higher than that of all deaths reported to NPSAD from England over the same period (16.0%; \( P < .01 \)). Looking at the sub-group of cases reported to NPSAD from England over the same period that were concluded as suicide, antihistamines were detected in 6.2% of these cases, with the proportion of suicides where an antihistamine was detected at postmortem on average rising year-on-year (Figure 4). This is despite the number of suicides in England generally
declining over the duration of the study period, as indicated both by total suicides reported to NPSAD (data not shown) and Office for National Statistics. Antihistamines were also implicated in a significantly larger proportion of suicides (42.4%; 136/321) than cases where death was deemed unintentional (33.0%; 335/1016, P < .01). In nearly half of all antihistamine-related suicides, diphenhydramine was the antihistamine most commonly detected (45.2% of cases; 145/321), followed by promethazine (24.0% of cases; 77/321) and cyclizine (18.4% of cases; 59/321). Acute drug use was deemed the underlying cause of death in 82.2% of antihistamine-related suicide cases (264/321) with the remainder due to environmental causes (e.g. asphyxiation, electrocution, fall from a height).

Whilst a single antihistamine was found at postmortem in the majority of cases (92.5%; 1421) they were seldom administered alone, with polydrug use evident in 98.5% of cases (1514). CNS depressants were the most commonly coadministered substances (94.8% of cases; 1457, Table 2), with opiates codetected in 73.5% of cases (1129), antidepressants in 56.2% (864), benzodiazepines/Z-drugs in 51.5% (725), and alcohol in 36.6% (562). Nearly half of antihistamine-related decedents were known to misuse drugs (44.1%, 678).

### Table 1
Number of cases reported to National Programme on Substance Abuse Deaths (England, 2000–2019) where each antihistamine was detected and the lowest category by which each antihistamine can be obtained. “Not licensed in the UK”

| Antihistamine      | Number of cases | Lowest obtainment category |
|--------------------|-----------------|----------------------------|
| First generation   |                 |                            |
| Promethazine       | 416             | P                          |
| Diphenhydramine    | 411             | P                          |
| Cyclizine          | 400             | P                          |
| Chlorpheniramine   | 174             | P                          |
| Hydroxyzine        | 97              | POM                        |
| Doxylamine         | 13              | P                          |
| Trimeprazine       | 5               | POM                        |
| Cinnarizine        | 4               | P                          |
| Brompheniramine    | 1               | -                          |
| Cyproheptadine     | 1               | -                          |
| Isothiependyl      | 1               | -                          |
| Tripolidine        | 1               | POM                        |
| Second generation  | 140             |                            |
| Cetirizine         | 101             | GSL                        |
| Loratadine         | 25              | GSL                        |
| Fexofenadine       | 7               | POM                        |
| Desloratadine      | 6               | POM                        |
| Mizolastine        | 1               | POM                        |
| Unknown            | 2               | -                          |

GSL, general sales licence; P, pharmacy; POM, prescription-only medication

The proportion of male decedents is significantly higher than that of female decedents for each antihistamine class, and overall (Table 3; all P < .01). However, when compared to all NPSAD cases...
from England reported in the same period, the proportion of males is significantly lower, and that of females significantly higher (Table 3; \( P < .01 \)). In all antihistamine-related cases, male decedents were on average significantly younger than females (Table 3; \( P < .01 \), 41.4 vs. 45.2).

4 | DISCUSSION

Despite first- and second-generation antihistamines being well established medications in the UK drug market for several decades, the proportion of internet searches in the UK for the term antihistamine has more than quadrupled in just the past 10 years.27

### Table 2: Number of cases reported to National Programme on Substance Abuse Deaths (England, 2000–2019) with an antihistamine and central nervous system (CNS) depressant codetected at postmortem

| Classification | Percentage of cases (n) |
|----------------|-------------------------|
| Total cases with a CNS depressant | 90.7% (1394) |
| Codetection with 1 CNS depressant class | 26.4% (405) |
| Opiate | 8.8% (136) |
| Antidepressant | 4.3% (66) |
| Alcohol | 4.1% (63) |
| Anxiolytic/sedative | 2.0% (30) |
| Codetection with 2 CNS depressant classes | 38.2% (587) |
| Opiate & antidepressant | 11.5% (176) |
| Opiate & Anxiolytic/sedative | 10.5% (162) |
| Opiate & alcohol | 5.6% (86) |
| Antidepressant & alcohol | 3.5% (54) |
| Antidepressant & anxiolytic/sedative | 2.5% (39) |
| Anxiolytic/sedative & alcohol | 2.1% (33) |
| Codetection with 3 CNS depressant classes | 26.2% (402) |
| Opiate & antidepressant & anxiolytic/sedative | 18.6% (286) |
| Opiate & antidepressant & alcohol | 5.5% (84) |
| Opiate & alcohol & anxiolytic/sedative | 5.4% (83) |
| Antidepressant & anxiolytic/sedative & alcohol | 2.8% (43) |
| Codetection with all 4 CNS depressant classes | 7.5% (116) |

4.1 | Pharmacy medicines predominate

The majority of the antihistamines detected were P medications. Motivation for P antihistamine misuse is likely to be 2-fold. Firstly, all P antihistamines detected belong to the first-generation sedating class of antihistamines, and there is concerning evidence to suggest that individuals are specifically seeking out P antihistamines for their sedative properties.28 Secondly, P medications can be legally purchased from a pharmacy without prescription in the UK.3 Whilst P medications still require supervision from a pharmacist for their dispensing, this barrier to obtainment is lower than those requiring a prescription making them an attractive option for those determined to misuse antihistamines.29–31 Furthermore, the number of community and online pharmacies in England have increased over the duration of the study period,32,33 which will have concomitantly increased P antihistamine availability. These compounding features have no doubt contributed to the listing of P antihistamines as 1 of the 5 medication groups of concern for OTC medicine misuse in an international review.34 By comparison, GSL antihistamines do not meet the first motivation criteria as GSL antihistamines comprise the second-generation non-drowsy class,1 and POM antihistamines do not meet the second motivation criteria as, by definition, a prescription is required for their dispensing.3 Reflective of this, the proportion of deaths where a GSL or POM antihistamine was detected is significantly smaller than those with a P antihistamine, this is even despite an overall rise in POM antihistamine prescribing. Whilst antihistamines are theoretically without abuse potential,6 the data presented here contribute to growing evidence of their misuse.

Specifically, there is growing concern regarding the misuse of promethazine,35–39 which is further deepened by the data presented here. Promethazine has a greater number of indications for which it can be purchased OTC (allergy treatment, travel sickness, night cold preparations)40 in comparison to other P antihistamines such as diphenhydramine and chlorpheniramine.41,42 Furthermore, recommended promethazine dosages and pack sizes vary by factors of

### Table 3: Sex and age at time of death in antihistamine-related cases reported to National Programme on Substance Abuse Deaths (NPSAD; England, 2000–2019)

| Antihistamine class | % male (n) | Mean age ±SD | % female (n) | Mean age ±SD |
|---------------------|------------|--------------|--------------|--------------|
| POM                 | 67.5% (79) | 41.5 ± 13.7  | 32.5% (38)  | 44.6 ± 12.8  |
| P                   | 56.7% (804)| 41.3 ± 12.6  | 43.3% (615) | 45.0 ± 13.4  |
| GSL                 | 61.2% (76) | 43.2 ± 15.5  | 38.7% (48)  | 46.3 ± 15.2  |
| Total antihistamine cases | 59.3% (911) | 41.4 ± 12.8  | 40.7% (626) | 45.2 ± 13.8  |
| All England NPSAD cases | 73.30% | 38.6 ± 0.1   | 26.70% | 44.2 ± 0.2   |

GSL, general sales licence; P, pharmacy; POM, prescription-only medication; SD, standard deviation
250 and 350%, respectively, depending upon the preparation purchased: a single 20-mg Sominex tablet (16 tablets per pack) is recommended for induction of sleep (Teva UK Limited, 2018), whilst up to 2 25-mg Phenergan tablets (56 tablets per pack) are recommended for the same indication. Phenergan Elixir is also available in a 5 mg/5 mL liquid formulation, which introduces the potential for inadvertent dosing error and also increases accessibility for those seeking to intentionally consume more than the recommended dose. This increased OTC availability may, therefore, be facilitating promethazine diversion for illicit nonmedical use. Indeed, the misuse and abuse potential of promethazine was recognised by the Danish Government in 2014, whereupon its accessibility was upgraded from OTC to POM.

A classification review of first-generation sedating antihistamines currently available as P medications, with specific regard to promethazine, is urgently needed in the UK. Indeed, there is evidence to suggest that some pharmacists are already taking matters into their own hands, hiding P antihistamines from open display (particularly promethazine) and refusing their sale.

### 4.2   A predilection for polypharmacy

Whilst antihistamine misuse has been documented to take place in combination with other substance use, concurring with patterns observed in other illicit drug users, the proportion of antihistamine-related decedents who coadministered a CNS depressant is still astounding. As promethazine is purported to potentiate the high from opioids, this drug–drug interaction is potentially being specifically sought by opioid users: patients on methadone maintenance therapy in a US study were reported to use promethazine for nonmedical reasons, injecting drug users in a Nepal study found that promethazine was administered alongside opioids and benzodiazepines in what is colloquially known as the South Asian Cocktail, and promethazine is combined with codeine to create the recreational drink preparation Purple Drank in the USA and Europe (also known as Sizzurp or Lean). These polypharmacy practices are reflected both in the growing number of promethazine-related deaths presented here, and the high rate of opioid coadministration. Furthermore, it is possible that individuals seeking to enhance effects of opioids may be using promethazine to replace the gabapentinoids, which have also been cited as potentiating the opioid high, as these compounds were put under additional controls in the UK in April 2019.

Although the British National Formulary states the interaction between sedating antihistamines and other CNS depressants is mild, the data presented here demonstrate that the additive effects of antihistamines in combination with multiple CNS depressants can prove fatal. As almost half of decedents were known to misuse drugs, healthcare and other supporting professionals should be including antihistamines in their warnings regarding CNS depressant misuse to poly substance users.

### 4.3   A problem of perception?

Antihistamines are a common feature of home first aid kits, and are routinely taken by infants, children, adults and elderly individuals for the wide-ranging indications for which they are designed. Trust from the general public in the use of antihistamines is probably borne out of the favourable safety profile of GSL nondrowsy second-generation antihistamines. However, the differences between first- and second-generation antihistamines, specifically the increased risk of over-sedation associated with first-generation compounds, are not broadly apparent to lay members of the public. Indeed, unintentional death due to acute polydrug use is clearly evident as a main underlying cause of death in cases where antihistamines were detected. This is further highlighted by a recent trend for individuals in the USA to post films of themselves on the social media platform TikTok after having taken large doses of the first-generation antihistamine diphenhydramine, which is available GSL in the USA. Furthermore, recreational misuse of the first-generation antihistamine promethazine is evident from its inclusion in the drink preparation Purple Drank. This perceived favourable safety profile may also be influencing interpretation of toxicology results by pathologists and coroners, given the apparent decreasing trend for implication of antihistamines in causing death: coadministration of more dangerous CNS depressants such as opioids and benzodiazepines may be causing the contribution of antihistamines to be overlooked. The global focus on opioids, whilst essential, might be distracting from a more holistic assessment.

Normalisation of acute antihistamine consumption may also be encouraging their chronic use for persistent insomnia, leading to the masking of serious conditions that can masquerade as sleep problems, such as anxiety and depression. Such antihistamine misuse would delay or completely obstruct critical investigations into the underlying root cause of the insomnia.

### 4.4   Prevalence in suicide

Whilst a significant proportion of antihistamine-related deaths were concluded as suicide, the true proportion is probably higher than that reported and therefore of even greater concern: a significant proportion of deaths concluded as undetermined intent are likely to have been suicide; there is an increasing trend for deaths to be recorded as narrative conclusions, and suicide poisonings are thought to sometimes be misclassified as accidental. The proportion of suicides involving an antihistamine is comparable to that reported elsewhere, as are the high prevalence of both diphenhydramine and promethazine. This indicates that awareness of the potentially dangerous sedative properties of first-generation antihistamines is heightened in individuals contemplating suicide, and is reflected in the high proportion of cases in this study where antihistamine use was implicated as an underlying cause of death. Access to means of suicide is a proximal determinant of whether someone will die by suicide. Restricting access can be an effective suicide prevention activity, as
was observed with paracetamol pack size restrictions. A review on the involvement of antihistamines in suicide is required for appropriate and effective measures to be taken to action harm reduction of antihistamines in suicide.

4.5 | Potential pharmacogenomic differences in pharmacokinetics

It is well documented that males are more likely to use all types of illicit drugs, with females more likely to misuse sedatives; trends that are also observed in the data presented here. Of interest, however, is the significant difference in mean age at time of death, with females on average being older. Limited data are available with regards to age- and sex-related differences in antihistamine pharmacokinetics. Retrospective pre-clinical and population pharmacokinetic analysis with regards to pharmacogenomic differences in antihistamine metabolism would be of benefit to enhance understanding of antihistamine age- and sex-dependent differential safety profiles.

4.6 | Limitations

Antihistamine-related deaths are probably under-reported. This is because, despite antihistamines being routinely tested for in UK toxicology tests, there is no standard and comprehensive range of antihistamines tested for between laboratories. It is possible for antihistamines to be detected retrospectively, which would enable antihistamine-related death figures to be more accurate. However, this would require manual re-evaluation and require availability of decedents’ biological samples. Furthermore, as NPSAD is reported to voluntarily and postmortems with toxicology tests are not carried out for all deaths, the figures presented here probably underrepresent the true number of antihistamine-related deaths occurring in England.

5 | CONCLUSIONS

This is the first report regarding antihistamine-related mortality from England. The rising trend in antihistamine-related deaths, particularly involving first-generation compounds, may, in part, be contributed to by a fall in the perceived dangers associated with antihistamine administration, both from the general public and learned professionals. Awareness of these potentially dangerous sedative properties is, however, heightened in individuals who are deliberately seeking out this effect. An urgent review of first-generation antihistamines currently assigned under the P classification, with special attention to promethazine, is needed to achieve antihistamine harm reduction. Dependent upon the assessed risk vs. benefit profile of individual antihistamines, recommendations including reclassification to POM status, limitations on quantity per pack, prominent warning labels or the requirement of a formal pharmacist consultation before access to these compounds is granted, could contribute towards achieving this aim.

ACKNOWLEDGEMENTS

The authors would like to thank Hugh Claridge and Christine Goodair for their ongoing advice and support of NPSAD. No funding source.

COMPETING INTERESTS

The authors have no conflicts of interest.

CONTRIBUTORS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Oyekan and Copeland. The first draft of the manuscript was written by Oyekan and Gorton, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the Principal Investigator. The data are not publicly available due to privacy restrictions.

ETHICS APPROVAL

The Central Office for Research Ethics Committees (COREC), of the National Patient Safety Agency confirmed (February 2006) that the NPSAD Programme does not require NHS Research Ethics Committee review as the subjects of the research are deceased. Neither the General Data Protection Regulation (GDPR) nor the Data Protection Act apply to identifiable data that relate to a person once they have died.

REFERENCES

1. Church MK. Allergy, Histamine and Antihistamines. Handb Exp Pharmacol. 2017;241:321–331.
2. Brown RE, Stevens DR, Haas HL. The physiology of brain histamine. Prog Neurobiol. 2001;63(6):637–672.
3. Kaliner MA, Check WA. Non-sedating antihistamines. Allergy Proc. 1988;9(6):649–663.
4. UK Medicines Act. 1968.
5. Veronika C, Aron F, Peter S. Safety risks of over-the-counter (OTC) drugs and their management. Acta Pharm Hung. 2016;86(4):151–159.
6. Reeves RR, Ladner ME, Perry CL, Burke RS, Laizer JT. Abuse of medications that theoretically are without abuse potential. South Med J. 2015;108(3):151–157.
7. Hedegaard H, Bastian BA, Trinidad JP, Spencer MR, Warner M. Regional Differences in the Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2017. Natl Vital Stat Rep. 2019;68(12):1–16.
8. Kang AM. Substances Involved in Suicidal Poisonings in the United States. Suicide Life Threat Behav. 2019;49(5):1307–1317.
9. Spiller HA, Ackerman JP, Smith GA, et al. Suicide attempts by self-poisoning in the United States among 10–25 year olds from 2000 to 2018: substances used, temporal changes and demographics. Clin Toxicol (Phila). 2020;58(7):676–687.
10. Kim E, Park Y, Ha H, Chung H. Patterns of drugs & poisons in southern area of South Korea in 2014. Forensic Sci Int. 2016;269:50–55.

11. Jang HS, Kim JY, Choi SH, et al. Comparative analysis of acute toxic poisoning in 2003 and 2011: analysis of 3 academic hospitals. J Korean Med Sci. 2013;28(10):1424–1430.

12. Jones AW, Holmgren A, Ahlner J. Toxicology findings in suicides: concentrations of ethanol and other drugs in femoral blood in victims of hanging and poisoning in relation to age and gender of the deceased. J Forensic Leg Med. 2013;20(7):842–847.

13. Jönsson AK, Holmgren P, Druid H, Ahlner J. Cause of death and drug use pattern in deceased drug addicts in Sweden, 2002-2003. Forensic Sci Int. 2007;169(2-3):101–107.

14. Hopkins RE, Dobbin M, Pilgrim JL. Intentional mortality associated with paracetamol and codeine preparations, with and without doxylamine, in Australia. Forensic Sci Int. 2018;282:122–126.

15. Ichikura K, Okumura Y, Takeuchi T. Associations of Adverse Clinical Course and Ingested Substances among Patients with Deliberate Drug Poisoning: A Cohort Study from an Intensive Care Unit in Japan. PLoS One. 2016;11(8):e0161996.

16. Serper M, Wolf MS, Parikh NA, Tillman H, Lee WM, Ganger DR. Risk Factors, Clinical Presentation, and Outcomes in Overdose With Acetaminophen Alone or With Combination Products: Results From the Acute Liver Failure Study Group. J Clin Gastroenterol. 2016;50(1):85–91.

17. Lev R, Petro S, Lee A, et al. Methadone related deaths compared to all prescription related deaths. Forensic Sci Int. 2015;257:347–352.

18. Deaths related to drug poisoning in England and Wales: 2018 registrations. UK: Office for National Statistics; 2019.

19. Fraser NC. Accidental poisoning deaths in British children 1958-77. Br Med J. 1980;280(6231):1595–1598.

20. www.gov.uk. When a death is reported to a coroner. Accessed November 2020.

21. Edwards S, Kitaoka H, Stein K, et al. A Systematic Review of the Current State of Knowledge on the Use of Over-the-Counter Medications in Inpatient Mental Health Settings. J Anal Toxicol. 2014;38(8):495–506.

22. Engelhart DA, Jenkins AJ. Comparison of drug concentrations in post-mortem cerebrospinal fluid and blood specimens. J Anal Toxicol. 2007;31(9):581–587.

23. OpenPrescribing. 2020. Available from: https://openprescribing.net/. Accessed September 2020.

24. BNF. British National Formulary 79: April 2020- March 2021. British National Formulary; 2020.

25. Mackridge A, Scott J, Cooper R. Time to rethink our approach to misuse of over the counter medicines. Pharm J. 2013;290:107.

26. Suicides in England and Wales: 2019 registrations. UK: Office for National Statistics; 2020.

27. GoogleTrends. Antihistamine 2020. Accessed September 2020.

28. Wright J, Bond C, Robertson HD, Matheson C. Changes in over-the-counter drug misuse over 20 years: perceptions from Scottish pharmacists. J Public Health (Oxf). 2016;38(4):793–799.

29. Lessenger JE, Feinberg SD. Abuse of prescription and over-the-counter medications. J Am Board Fam Med. 2008;21(2):45–54.

30. Hughes CM, McElney JC, Fleming GF. Benefits and risks of self medication. Drug Saf. 2001;24(14):1027–1037.

31. Bond C, Hannaford P. Issues related to monitoring the safety of over-the-counter (OTC) medicines. Drug Saf. 2003;26(15):1065–1074.

32. Mikulic M. Community pharmacies in England 2006–2019. Statista; 2019.

33. Mikulic M. Number of Distance Selling/Mail Order pharmacies in England from 2008/09 to 2018/19. Statista; 2019.

34. Cooper RJ. Over-the-counter medicine abuse - a review of the literature. J Subst Use. 2013;18(2):82–107.

35. Tsay ME, Procopio G, Anderson BD, Klein-Schwartz W. Abuse and Intentional Misuse of Promethazine Reported to US Poison Centers: 2002 to 2012. J Addict Med. 2015;9(3):233–237.

36. Shapiro BJ, Lynch KL, Toochinda T, Lutnick A, Cheng HY, Kral AH. Promethazine misuse among methadone maintenance patients and community-based injection drug users. J Addict Med. 2013;7(2):96–101.

37. Lynch KL, Shapiro BJ, Coffa D, Novak SP, Kral AH. Promethazine use among chronic pain patients. Drug Alcohol Depend. 2015;150:92–97.

38. Miuli A, Stigliano G, Lalli A, et al. “Purple Drank” (Codeine and Promethazine Cough Syrup): A Systematic Review of a Social Phenomenon with Medical Implications. J Psychoactive Drugs. 2020;52:453–462.

39. Chiappini S, Schifano F, Corkery JM, Guirguis A. Beyond the purple drank: Study of promethazine abuse according to the European medicines agency (EMA) adverse drug reactions (ADR) reports. J Psychopharmacol. 2021 In press. https://doi.org/10.1177/0269881120959615

40. Southard BT, Al Khalili Y. Promethazine. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2020.

41. Sicari V, Zabbo CP. Diphenhydramine. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2020.

42. Rumore MM. Clinical pharmacokinetics of chlorpheniramine. Drug Intell Clin Pharm. 1984;18(9):701–707.

43. Sanofi. Phenergan 25 mg tablets. Electronic Medicines Compendium. 2019.

44. Sanofi. Phenergan Elixir. Electronic Medicines Compendium. 2020.

45. Joshi P, Bavdekar SB. Liquid Drug Dosage Measurement Errors with Different Dosing Devices. Indian J Pediatr. 2019;86(4):382–385.

46. Promethazine status changes to prescription-only in Denmark. Promethazine status changes to prescription-only in Denmark. React WM. 2015;1535(1):4.

47. Olja SP, Sigdel S, Meyer-Thompson HG, Oechsler H, Verthein U. “South Asian cocktail”–the concurrent use of opioids, benzodiazepines and antihistamines among injecting drug users in Nepal and associations with HIV risk behaviour. Harm Reduct J. 2014;11(1):17.

48. Hickman M, Carrick S, Paterson S, et al. London audit of drug-related overdose deaths: characteristics and typology, and implications for prevention and monitoring. Addiction. 2007;102(2):317–323.

49. Lyndon A, Audrey S, Wells C, et al. Risk to heroin users of polydrug use of pregabaline or gabapentin. Addiction. 2017;112(9):1580–1589.

50. Sánchez-Borges M, Anagnostou E. Second generation antihistamines: an update. Curr Opin Allergy Clin Immunol. 2019;19(4):358–364.

51. Church MK, Maurer M, Simons FE, et al. Risk of first-generation H1-antihistamines: a GA(2)LEN position paper. Allergy. 2015;70(7):949–980.

52. Treasure Island (FL): StatPearls Publishing; 2020.

53. Tsay ME, Procopio G, Anderson BD, Klein-Schwartz W. Abuse and Intentional Misuse of Promethazine Reported to US Poison Centers: 2002 to 2012. J Addict Med. 2015;9(3):233–237.

54. Shapiro BJ, Lynch KL, Toochinda T, Lutnick A, Cheng HY, Kral AH. Promethazine misuse among methadone maintenance patients and community-based injection drug users. J Addict Med. 2013;7(2):96–101.

55. Lynch KL, Shapiro BJ, Coffa D, Novak SP, Kral AH. Promethazine use among chronic pain patients. Drug Alcohol Depend. 2015;150:92–97.

56. Gunnell D, Lewis G. Studying suicide from the life course perspective: implications for prevention and monitoring. Addiction. 2007;102(2): 317–323.

57. Hawton K, Bergen H, Simkin S, et al. Long term effect of reduced activity in England and Wales: interrupted time series analyses. BMJ: Br Med J. 2013;346:f403.
58. NIDA. Sex and Gender Differences in Substance Use. 2020. Available from: https://www.drugabuse.gov/publications/research-reports/substance-use-in-women/sex-gender-differences-in-substance-use. Accessed September 2020.

59. Nicolas JM, Espie P, Molimard M. Gender and interindividual variability in pharmacokinetics. Drug Metab Rev. 2009;41(3):408–421.

60. Friedman H, Greenblatt DJ, Scavone JM, et al. Clearance of the antihistamine doxylamine. Reduced in elderly men but not in elderly women. Clin Pharmacokinet. 1989;16(5):312–316.

61. Alexander SPH, Christopoulos A, Davenport AP, et al. THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: G protein-coupled receptors. Br J Pharmacol. 2019;176(Suppl 1):S21–s141.

How to cite this article: Oyekan PJ, Gorton HC, Copeland CS. Antihistamine-related deaths in England: Are the high safety profiles of antihistamines leading to their unsafe use? Brit J Clin Pharmacol. 2021;1–10. https://doi.org/10.1111/bcp.14819