J. Med. Toxicol. (2012) 8:300–303
DOI 10.1007/s13181-012-0241-3

REVIEW ARTICLE

Understanding How Data Triangulation Identifies Acute Toxicity of Novel Psychoactive Drugs

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Published online: 12 May 2012

Abstract Over the last decade, there has been an increase in the availability and use of novel psychoactive substances (also known as "legal highs"). There is limited information available on the potential acute toxicity (harms) associated with the use of these novel psychoactive substances. Gold standard evidence, such as animal studies or human clinical trials, is rarely available to users or healthcare professionals. However, it is possible to use triangulation of data on the acute toxicity from multiple sources to describe the overall pattern of toxicity associated with a novel psychoactive substance. In this review, we will describe these potential data sources, which include self-reported toxicity on internet discussion fora, data from sub-population user surveys, data from regional and national poisons information services and published case reports and case series. We will then describe how pattern of acute toxicity associated with the use of the cathinone mephedrone (4-methylmethcathinone) was established using triangulation of these different data sources.

Keywords Recreational drugs · Novel pyschoactive substances · Acute toxicity · Harm

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Introduction

There has been an increasing use of substances known as novel psychoactive substances (legal highs) on the recreational drug scene over the last decade [1–5]. Often, there is little published data available to users or healthcare professionals on the potential acute toxicity (harm) associated with the use of novel psychoactive substances. They are typically labelled "not for human consumption", and suppliers therefore do not include information to the intended user on their potential unwanted effects. Additionally, marketing as legal highs or "herbal highs" may suggest to users that these compounds are less likely to be associated with the same acute toxicity as that seen with the use of established recreational drugs.

There is the need to accurately describe the pattern(s) of acute toxicity following human use, not only for healthcare professionals managing these individuals but also for legislative authorities to ensure that these substances are appropriately controlled. In this mini-review, we will summarise how, using triangulation of data from a number of different sources, it is possible to develop an overall picture of the pattern of toxicity associated with an individual novel psychoactive substance, which reduces the impact of the limitations of any individual data source. We will use mephedrone (4-methylmethcathinone) to illustrate how the process of data triangulation can be used to describe the overall pattern of toxicity of a novel psychoactive substance.

Potential Sources of Information on Acute Toxicity

The gold standard for describing the pattern of acute toxicity associated with the use of a novel psychoactive substance would be detailed animal and/or human trials studying

pharmacokinetic and pharmacodynamic properties of the substance. However, information such as this is rarely available for these substances; therefore, we have to rely on a number of other data sources in an attempt to provide this information.

National and international population level surveys, such as the British Crime Survey, European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) annual report and the UNODC annual World Drug Report collect detailed data on the prevalence of use of established recreational drugs but only very limited data on the use of novel psychoactive substances [1, 6, 7]. However, these surveys do not provide information on the patterns of acute toxicity associated with the use of novel psychoactive substances. It is also not possible to routinely interrogate national hospital admission datasets, such as the UK Hospital Emergency Statistics, to identify presentations related to novel psychoactive substance-related acute toxicity. These datasets are based on international coding systems, such as the "International Classification of Diseases Version 10" (ICD-10); these are robust for diseases such as respiratory or cardiovascular disease but poor with regards to having appropriate codes for established recreational drug toxicity and have no appropriate coding mechanisms for novel psychoactive substances [8, 9].

Users of novel psychoactive substances often post information on both the desired and unwanted effects seen following use on internet discussion fora and blogs; examples of these include Erowid and Drugs forum [11, 12]. These user reports can often be very detailed, in some cases describing minute-by-minute physiological parameters and other desired/unwanted effects, along with information on the amount of substance used and the route(s) of use. Additionally, there is also the potential to undertake small sub-population level surveys to try and collate this information from a broader group of users [3–5, 10]. One example would be the annual MixMag drugs survey, which is conducted through the MixMag clubbing magazine and internet site [5]. It is designed to capture data on trends in the use of recreational drugs and novel psychoactive substances; however, those conducting the survey often include additional questions relating to the acute harm associated with the use of drugs and novel psychoactive substances. Both of these approaches are limited in that they are based on anecdotal self-reported use and harms, and therefore there is no analytical confirmation of the substance(s) used. In addition, the sub-population surveys often used predetermined unwanted effects to facilitate data analysis but which may limit any additional responses.

The initial information on acute toxicity from a medical perspective is often based on single case reports or case series. Previously, a significant proportion of these were based on self-reported use of a substance and then on correlation with the symptoms and signs on or prior to presentation to medical services. However, there is increasing evidence from studies in the UK, Europe and the USA that there is significant variability in the contents of novel psychoactive substances [13–16]. Therefore, it is important that these case reports/case series should include toxicological analysis of biological samples to confirm the substance (s) used and also to exclude other substances which may explain the symptoms/signs reported. This often requires involvement of clinicians with an interest in the management of acute novel psychoactive substance toxicity supported by appropriately funded and equipped analytical facilities to identify novel psychoactive substances.

In many European countries, in the USA and other countries in the world, there is provision of poisons information services to healthcare professionals and/or members of the public. There is the potential to utilise information on accesses (e.g. calls to telephone services, "hits" on Internet pages) to these services to try and determine some marker of the trends in the reporting of acute harm associated with novel psychoactive substances; additionally, it is possible to collect more detailed information on the associated symptoms/signs. There are a number of limitations with these datasets. Firstly, both the individual presenting with acute recreational drug toxicity and the healthcare professional may not be aware that the presentation relates to a novel psychoactive substance. Secondly, there is the potential that there may be misinterpretation of the substance used. This was commonly seen in the UK when mephedrone entered the recreational drug scene, and initially people mistakenly recorded it as the sound-alike, but pharmacologically and toxicologically very different, methadone. Finally, it requires someone to access the poisons information service and to both recognise and report the use of the novel psychoactive substance.

There is one additional overriding caveat for all of these alternative data sources. They all require that a novel psychoactive substance has been used by individuals for a period of time before the information starts to become available from these different data sources, to allow subsequent data triangulation to be undertaken.

Despite the limitations described above, data from these sources can be useful in helping to put together a picture on the potential for and/or the actual toxicity associated with the use of novel psychoactive substances. We will now describe, using the example of mephedrone (4-methylmethcathinone), how data triangulation from these sources can be used, reducing the impact of the limitations of any one individual data source.

Acute Mephedrone-Related Toxicity: An Example of Data Triangulation

Mephedrone, 4-methylmethcathinone, is a novel psychoactive substance that entered the European recreational drug scene in 2008, with increasing frequency of use in 2009 and 2010.

Currently, there are no national or international surveys collecting information on the acute toxicity associated with the use of mephedrone. Additionally, at this time, there is no ICD-10 specific code for acute mephedrone toxicity, and therefore it is not possible to interrogate hospital admission databases to determine the frequency of hospital admissions.

There are numerous reports on different internet discussion fora describing the unwanted effects in relation to self-reported mephedrone use [17–19]. Commonly reported unwanted effects include elevated body temperature, chest pain, convulsions, anxiety, sweating, hallucinations, paranoia, bruxism and elevated heart rate and blood pressure. When these individual reports are combined, the overall pattern of described unwanted effects would be consistent with the acute sympathomimetic drug toxicity.

The 2009 MixMag survey collected information from 900 individuals who self-reported previous use of mephedrone on the unwanted effects that they had experienced with its use [5, 20]. The unwanted effects seen were the following: sweating (67.2 % of those who reported previously using mephedrone), headaches (50.7 %), palpitations (43.4 %), nausea (37.0 %) and cold/blue fingers (15.3 %). In a study of Scottish school and college/university aged students, 56 % reported that they had experienced at least one unwanted effect related to the use of mephedrone [10]. The unwanted effects included bruxism (28.3 % of users), paranoia (24.9 %), hot flushes (23.4 %), palpitations (20.5 %), hallucinations (18.0 %), as well as direct irritation effects related to its use (sore nasal passages 24.4 %, nose bleeds 22.4 %).

Data from Swedish Poisons Information Service described 150 calls in 2008/2009 relating to the use of cathinones, which included mephedrone [21]. Reported symptoms/signs were tachycardia (54 % of cases), restlessness (37 %), mydriasis (25 %), hypertension (14 %) and anxiety (14 %). A subsequent report on 131 telephone enquiries to the UK National Poisons Information Service, reported that the most commonly reported clinical features were agitation/aggression (24 % of calls), tachycardia (22 %), anxiety (15 %), confusion or psychosis (14 %), chest pain (13 %), palpitations (11 %) and nausea (11 %) [22]. Convulsions were reported to have only occurred in 4 % of cases and myoclonus in 2 %.

There have been a number of case reports and case series of individuals presenting to an emergency department with mephedrone-related acute toxicity [23–27]. The first analytically confirmed case of recreational mephedrone use was in an individual who presented feeling generally unwell with chest tightness, sweating and palpitations [25]. There have been two large UK emergency department-based case series of acute mephedrone toxicity, one from Aberdeen and the other from London [23, 26, 27]. In a 4-month period in a Scottish emergency department, there were 89 presentations related to self-reported mephedrone use [26]. The clinical symptoms/signs in the 57 who self-reported lone mephedrone or combined mephedrone/ethanol use included anxiety/agitation (40.4 %), chest pain (24.6 %), parasthesiae (24.6 %), palpitations (21.1 %), dyspnoea (17.5 %) and confusion (17.5 %). Seventy-nine percent had a tachycardia (defined as a heart rate of >90 beats per minute), and 74 % of patients had hypertension (systolic BP >130 mmHg). The most common unwanted effect in our London case series was agitation (38.9 %) and other commonly reported features were palpitations (25.0 %), vomiting (13.9 %), chest pain (12.5 %), self-limiting prehospital seizures (6.9 %) and headache (7.2 %) [23, 27]. A 13.9 % of patients had clinically significant hypertension (defined as a systolic blood pressure ≥160 mmHg), 36.1 % had a tachycardia (heart rate of ≥100 bpm) and 8.3 % had a severe tachycardia (≥140 bpm). In a subset of seven patients with analytically confirmed mephedrone use, the unwanted effects included agitation (57.1 %), palpitations (28.6 %), chest pain (28.6 %), self-limiting pre-hospital seizures (14.3 %) and headache (14.3 %); 42.9 % had clinically significant hypertension, 71.4 % of had a tachycardia and 14.3 % had a severe tachycardia [24].

When these different data sources are combined, the overall picture of acute toxicity associated with the use of mephedrone is consistent with that seen with the use of other sympathomimetic recreational drugs such as amphetamine, cocaine and MDMA ("ecstasy").

Conclusions

The range of novel psychoactive substances is increasing over time, and the overriding challenge is to provide users, healthcare professionals and legislative authorities with an accurate description of the pattern of acute toxicity, and where possible, to ensure that this is based on analytical confirmation of the substance(s) used. It is possible to triangulate data from a variety of sources in an attempt to provide an overall pattern of acute toxicity related to the use of an individual novel psychoactive substance. Each source has its own limitations, but triangulation of different data sources with different limitations allows greater overall precision in the description of the pattern of acute toxicity. There needs to be a more combined, appropriately funded approach to undertake triangulation of these data sources to ensure that users and healthcare professionals are aware of the actual patterns of acute harms, and so that legislative authorities can base drug classification decisions on accurate information.

Conflicts of Interest DMW and PID have acted as expert advisors to the UK Advisory Council on the Misuse of Drugs and the European Monitoring Centre for Drugs and Drugs Addiction (EMCDDA) on issues related to established recreational drugs and novel psychoactive substances.

References

1. Home Office Statistical Bulletin (2011) Drug misuse declared: findings from the 2010/11 British Crime Survey http://www.homeoffice.gov.uk/publications/science-research-statistics/research-statistics/crime-research/hosb1211/hosb1211?view=Binary [Last accessed 19th April 2012]
2. Wood DM, Ramsey J, Dargan PI (2008) Detecting novel and emerging recreational drugs on the 'club scene'. Irish Psychiatrist 9:223–228
3. Wood DM, Measham F, Dargan PI (2012) 'Our Favourite drug': prevalence of use and preference for mephedrone in the London night time economy one year after control. J Subs Use 17:91–97
4. Measham F, Wood DM, Dargan PI, Moore K (2011) The rise in legal highs: prevalence and patterns in the use of illegal drugs and first and second generation 'legal highs' in south London gay dance clubs. J Subs Use 16:263–272
5. Dick D, Torrance C (2010) Drugs survey. Mixmag 225:44–53
6. EMCDDA Annual Report 2011: Annual report on the state of the drugs problem in Europe (2011). http://www.emcdda.europa.eu/attachements.cfm/att_143743_EN_EMCDDA_AR2011_EN.pdf [Last accessed 19th April 2012]
7. UN World drug report 2011. (2011) http://www.unodc.org/documents/data-and-analysis/WDR2011/World_Drug_Report_2011_ebook.pdf [Last accessed 19th April 2012]
8. Shah A, Wood DM, Dargan PI (2011) Survey of ICD-10 coding of hospital admissions in the UK due to recreational drug toxicity. Q J Med 104:779–784
9. Wood DM, Conran P, Dargan PI (2010) ICD-10 coding: poor identification of recreational drug presentations to a large emergency department. Emerg Med J 28:387–389
10. Dargan PI, Albert S, Wood DM (2010) Mephedrone use and associated adverse effects in school and college/university students before the UK legislation change. Q J Med 103:875–879
11. Erowid. Documenting the complex relationship between humans and psychoactives. www.erowid.org [Last accessed 19th April 2012]
12. Drugs Forum. http://www.drugs-forum.com/index.php [Last accessed 19th April 2012]
13. Ramsey J, Dargan PI, Smyllie M, Davies S, Button J, Holt DW, Wood DM (2010) Buying "legal" recreational drugs does not mean that you aren't breaking the law. Q J Med 103:777–783
14. Davies S, Wood DM, Smith G, Button J, Ramsey J, Archer R, Holt DW, Dargan PI (2010) Purchasing "legal highs" on the internet—is there consistency in what you get? Q J Med 103:489–493
15. Brandt SD, Sumnall HR, Measham F, Cole J (2010) Analyses of second-generation 'legal highs' in the UK: initial findings. Drug Test Anal 2:377–382
16. Spiller HA, Ryan ML, Weston RG, Jansen J (2011) Clinical experience with and analytical confirmation of "bath salts" and "legal highs" (synthetic cathinones) in the United States. Clin Toxicol (Phila) 49:499–505
17. Erowid experience vaults: 4-methylmethcathinone reports (including mephedrone, 4-MMC, Meow and M-cat). https://www.erowid.org/experiences/subs/exp_4Methylmethcathinone.shtml [Last accessed 19th April 2012]
18. Mephedrone and Beta-Ketones. http://www.drugs-forum.com/forum/forumdisplay.php?f=377 [Last accessed 19th April 2012]
19. Psychonaut WebMapping Research Group 2009, Mephedrone Report. Institute of Psychiatry, King's College London, London, UK. http://194.83.136.209/documents/reports/Mephedrone.pdf [Last accessed 19th April 2012]
20. Winstock AR, Mitcheson LR, Deluca P, Davey Z, Corazza O, Schifano F (2011) Mephedrone, new kid for the chop? Addiction 106:154
21. Hagerkvist R, Hulten P, Personne M (2010) Increasing abuse of new cathinone derivatives in Sweden—a poisons centre study for the years 2008–2009. Clin Toxicol 48:291
22. James D, Adams RD, Spears R, Cooper G, Lupton DJ, Thompson JP, Thomas SH, on behalf of the National Poisons Information Service (2011) Clinical characteristics of mephedrone toxicity reported to the UK National Poisons Information Service. Emerg Med J 28:686–689
23. Annex 1 to the Risk assessment report: TECHNICAL REPORT ON MEPHEDRONE. Prepared by Dr Paul Dargan and Dr David Wood, Guy's and St Thomas' NHS Foundation Trust, London, UK. EMCDDA contract CT.10.EPI.057. July 2010. http://www.ofdt.fr/BDD/publications/docs/rarOEDTmephAnn1.pdf [Last accessed 19th April 2012]
24. Wood DM, Davies S, Greene SL, Button J, Holt DW, Ramsey J, Dargan PI (2010) Case series of individuals with analytically confirmed acute mephedrone toxicity. Clin Toxicol (Phila) 48:924–927
25. Wood DM, Davies S, Puchnaewicz M, Button J, Archer R, Ovaska H, Ramsey J, Lee T, Holt DW, Dargan PI (2010) Recreational use of Mephedrone (4-methylmethcathinone, 4-MMC) with associated sympathomimetic toxicity. J Med Toxicol 6:327–330
26. Regan L, Mitchelson M, Macdonald C (2011) Mephedrone toxicity in a Scottish emergency department. Emerg Med J 28:1055–1058
27. Wood DM, Greene SL, Dargan PI (2011) Clinical pattern of toxicity associated with the novel synthetic cathinone Mephedrone. Emerg Med J 28:280–282