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EDITORIAL

The consequences of drug misuse on post-marketing surveillance

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Introduction

Over the past decade, the 'traditional' drug scenario has shown significant changes because of the emergence of a range of molecules, e.g. the novel psychoactive substances (NPS), which are either already existing or newly created molecules [1]. A range of prescribed medications are currently being used as NPS [1]. Overall, the misuse and diversion of medications is a significant and increasing public health concern [2], with 5.4% of British respondents aged 16–19 years old having abused a prescription drug in the past 12 months [3]. It is a matter of concern that, for a range of prescribing molecules (e.g. gabapentinoids), the formal pre-marketing processes had not been able to appropriately identify their potential for abuse, a potential which has however emerged overtime [4,5]. Similarly, drugs such as benzodiazepines and z-hypnotics were considered 'safe' for many years before their addictive liability levels were identified.

Hence, in this article, we aimed at commenting on the different factors relating to pre- and post-marketing prescription drugs' abuse liability assessment; issues likely to be complicated by recent changes in drug scenarios.

Pre-marketing assessment of the abuse liability of a new drug

For a new drug to be approved and to be considered 'safe', a range of abuse liability assessments are carried out, which are based on a multi-faceted profile of the drug's chemistry, pharmacology, clinical manifestations, similarity to other drugs in a class, and potential for public health risks [6]. Pre-marketing trials are designed to provide useful information on abuse liability levels [2,7–9]. However, these trials typically involve the administration of carefully controlled, daily limited, therapeutic dosages. A weakness of these trials is that subjects with a current/previous history of drug misuse/addiction are excluded [10]. As a consequence, the molecule's potential for abuse will be fully appreciated only when the real world client population, involving vulnerable individuals, is exposed to it [5].

Current and optimal post-marketing pharmacovigilance approaches to detect signals of abuse liability of a product

Challenges in pharmacovigilance database analyses

Spontaneous pharmacovigilance reports may play a major role in the identification of drugs' addictive liability levels. However, relevant data are often incomplete, and spontaneous reporters often use different terminologies and/or a range of terms in parallel [6]. Furthermore, the rate at which cases are reported is dependent on issues, such as: time since launch; existing regulatory activities; media attention; and literature reports [11]. A range of proxies of prescription drug misuse are typically being used across pharmacovigilance studies, including: number of prescribers, number of dispensing pharmacies, early refills, and volume of drugs dispensed [12]. Although monitoring trends in reporting patterns may improve signal detection, optimal approaches should consider a range of further methodological options [13], including the use of: (a) appropriate denominator data, e.g. considering the estimated number of people in the general population exposed to a given molecule; (b) calculation of the proportional reporting ratio (PRR). This is a measure of disproportionality of reporting, with a PRR greater than 1 suggesting that the adverse event is more commonly reported for individuals taking the drug of interest, relative to the comparison drug(s) [14]; (c) data mining algorithms, which are database screening tools used to distinguish proper 'signals', from 'noise' (e.g. data lacking of public health interest) [15]; and (d) Bayesian hierarchical models, helpful in analyzing a huge volume of adverse drug reaction (ADRs') data, with outputs being used in signal validation [16].

Role of post-marketing, multiple sources/social media, surveys

As a single source may not be informative enough, some surveillance programs (e.g. the French CEIP Addiction vigilance network) consider simultaneously a range of indicators, focusing on: suspicious prescriptions; range of misused

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prescribing psychotropics; health insurance databases; and health professional sentinel networks [17]. At a wider level, the Europe-wide toxicovigilance system monitors almost 600 NPS, including listed prescription drugs, identifying signals of related serious harms and responding through risk communication/risk assessment [18].

Although further data could derive from law enforcement; drug abuse treatment programs; poison centers; and medical emergency departments [19], one could wonder about how effective these agencies are at early detecting the abuse potential of psychotropics. In fact, it is only when the molecule's availability has reached a critical mass that the Police will be able to seize the molecule's first batches; relating near misses will present to the emergency rooms; and clients will start asking treatment agencies for help. An increase in online trafficking/debate on a specific psychoactive drug typically precedes the occurrence of clinical incidents at the population level [5,20,21]. Using an integrated web mapping/social media system, phenomena, such as abuse of both synthetic cannabimimetics/'spice' and synthetic cathinones were all identified as emerging trends at a time when very limited or no scientific publications were available [20]. With a similar web/social media-based approach, an extensive description of gabapentinoid addictive liability was provided at a time when the potential of pregabalin abuse was not even mentioned in the prescribers' aids [5].

The use of social media/web data for ADR monitoring, including assessment of search logs from healthcare professionals [22], is receiving increasing levels of attention [23]. The amount of user-generated data on social media and other Internet-based venues provides the possibility to systematically mine, aggregate, and analyze textual/unstructured data (e.g. 'infodemiology'), with 'infoveillance' being used for surveillance purposes [24]. Similarly, the 'netnography' [25] systematic approach provides an innovative methodology to collect online data on NPS/prescription drugs' abuse/misuse.

While considering the web-based approach, White et al. [26] analyzed search queries collected from 80 million consenting users and found that the ADR detection performance via search logs was comparable to the adverse event system detection of US FDA, even increasing accuracy levels by 19%. Finally, Sarker et al. [27] recently assessed Twitter users' posts as a resource for the automatic monitoring of prescription medication abuse. They found that, with a calculated 82% accuracy overall, the percentage of tweets containing abuse signals were significantly higher for the three case medications (Adderall 23%; quetiapine: 5%, oxycodone: 12%) than the proportion for the control medication (metformin: 0.3%). There are different approaches to ADR detection/extraction from web/social media; these include: supervised classification techniques (to detect posts containing ADR mentions) and lexicon-based approaches (for extraction of ADR mentions from texts, such as Tweets) [28].

What happens when the abuse potential of a drug has been identified? A few case studies

If during the post-marketing phase, a potential for abuse is identified, a range of risk management programs (RMPs) [6] are increasingly being required to address the regulatory agencies' concerns [29]. RMPs typically require the implementation of a 'risk minimization action plan', which may well include either enabling access to a drug only under highly restricted conditions or drug scheduling [30]. A few case studies, highlighting a range of different post-marketing situations, are illustrated below.

> Drugs with a limited potential for abuse where post-marketing measures are currently not being considered: olanzapine; quetiapine; venlafaxine; and tropicamide

Olanzapine, a popular second-generation antipsychotic (SGA), is being anecdotally identified online as the 'ideal trip terminator' after a psychedelic drug binge. The molecule is self-prescribed, and for a few days only, at very large daily dosages (e.g. up to 50 mg) [31,32]. Another SGA, *quetiapine* (*'Q ball'*), is anecdotally advised to help 'come off the psychedelic trip'. Vulnerable subjects (e.g. adolescents and inmates) may be particularly at risk [33]. Methods of quetiapine misuse include inhaling/injecting crushed tablets [34]. Reasons for abuse of atypical antipsychotics may include the desire of 'feeling mellow' [35].

Similar issues have been raised with *venlafaxine/'baby ecstasy'* [36,37], a popular antidepressant whose misuse is possibly related to the increase it produces in dopamine neurotransmission mainly at the prefrontal cortex level [38].

Conversely, changes in routes of administration are behind abuse of *tropicamide*, an ophthalmic anticholinergic compound which, when injected, may be associated with hallucinations, dysphoria, psychomotor agitation, tachycardia and suicidal ideation [39].

The abuse potential of the above molecules is not mentioned in the medications' package leaflet/patient information leaflet [40–43], and it has not been the subject of pharmacovigilance studies.

> Drugs possessing a clear potential of abuse where post-marketing measures have been/are being considered: gabapentinoids; oxycodone; and hydromorphone

Gabapentinoids are approved in Europe for the treatment of epilepsy/partial seizures and neuropathic pain, with pregabalin being licensed for generalized anxiety disorder as well [5]. In parallel with increasing prescribing levels, a growing black market is currently being observed [44]. Overall, pregabalin is characterized by higher potency, quicker absorption rates, and greater bioavailability than gabapentin [5]. Typical abusers of these compounds are individuals with a history of recreational polydrug use. Euphoria, improved sociability, opiate-like sedation, dissociation, and psychedelic effects are associated with gabapentinoid high/very high dosage intake. Intravenous use, rectal 'plugging' and smoking of pregabalin have also been reported [45], with opiates/opioids being frequently misused in combination [46]. Pregabalin has been approved in Canada and the United States, since 2005, and EU approval to treat generalized anxiety disorder was received in 2006 [47]. Yet, a proper debate regarding abuse and dependence did not start in the medical literature before 2010 [48]. In the United Kingdom, gabapentinoids are currently the subject to formal attention/rescheduling to prevent diversion and abuse [44].

Oxycodone

Its non-medical use is a relatively recent concern, especially in the United States [6] and Canada [47]. Because of the controlled-release formulation, at the time of approval its abuse potential was considered by FDA to be similar to other opioid analgesics. Crushing the controlled-release capsule, followed by intravenous injection or snorting, has however led to high levels of abuse [6]. As a result of this, an abuse-deterrent formulation was introduced in 2010 [49], and labeling changes were implemented.

Hydromorphone

The FDA approved this molecule in 2004 for the management of moderate/severe pain [6]. Eventually, a sponsor's study identified that, compared to taking hydromorphone alone, when co-administered with alcohol the blood hydromorphone concentrations were significantly higher [6]. Eventually, sales and marketing of the drug were suspended.

Conclusions

In this article, it is suggested that in Europe, much as is done in the United States, post-marketing surveillance for substance abuse is needed as a matter of routine to assess the abuse potential of newly released drugs with addictive liability levels (e.g. opiates/opioids; stimulants, etc.). Overall increasing levels of access to the web over the past 15 years or so may have contributed to the current scenario of prescribed drugs' abuse. Indeed, social networks may play a role in prescription drugs' aggressive marketing/distribution from rogue websites [50]. Furthermore, within the online drug fora communities, there are some educated/informed users who typically 'test' a range of psychotropics to achieve the state of consciousness they find most pleasurable, eventually making this information available to peers [51].

Guidelines have been drafted to carry out laboratory-based testing to improve post-marketing medications' abuse predictive ability [2,7–9]. However, overall failures of pre-marketing clinical trials in detecting a range of psychotropics' addictive potential [4] may have complicated the current scenario. Abuse liability-focused laboratory testing may need to consider interaction studies with alcohol and/or other drugs. Furthermore, tamper-resistant delivery systems need to be routinely considered [2,52].

Pharmaceutical manufacturers applying for approval of novel molecules with clearly identified levels of abuse (e.g. opiates/opioids, stimulants, etc.) could submit post-marketing plans for a strategy addressing education, prevention, detection and abuse/diversion issues. Post-authorization safety studies to monitor the effectiveness of any risk minimization measures would be desirable as well [6].

In the United Kingdom, many websites offering unauthorized medicines for sale have seen been shut down, but this has just shifted the sellers to servers in overseas countries, with a sort of 'playing catch up' scenario [53]. Since part of the problem is the demand, and not the supply, it may be unrealistic to design a reliable system to stop online medicine-related transactions [53].

Finally, while a continuum of related professional training is needed, it may be important to consider a strategy increasing clients' access to treatment services [54] possibly enhancing links between community pharmacists (first professionals to identify a repeat supplies' issue) and prescribers/clinicians.

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References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1. Schifano F, Orsolini L, Duccio Papanti G, et al. Novel psychoactive substances of interest for psychiatry. World Psychiatry. 2015;14:15–26.

•• **World Psychiatry: this is a thorough review of the different classes of novel psychoactive substances (NPS), including prescription drugs being used as NPS, with a particular focus on the psychopathological disturbances associated with their ingestion.**

2. Johanson C-E, Balster RL, Henningfield JE, et al. Risk management post-marketing surveillance for the abuse of medications acting on the central nervous system: expert panel report. Drug Alcohol Depend. 2009;105 Suppl 1:S65–S71.
3. Office for National Statistics. Crime in England and Wales: year ending March 2015; [cited 2016 Mar 7]. Available from: http://www.ons.gov.uk/peoplepopulationandcommunity/crimeandjustice/bulletins/crimeinenglandandwales/2015-07-16
4. Schifano F. Misuse and abuse of pregabalin and gabapentin: cause for concern? CNS Drugs. 2014;28:491–496.
5. Schifano F, D'Offizi S, Piccione M, et al. Is there a recreational misuse potential for pregabalin? Analysis of anecdotal online reports in comparison with related gabapentin and clonazepam data. Psychother Psychosom. 2011;80:118–122.
6. US Food and Drug Administration (FDA). FDA's Role in Preventing Prescription Drug Abuse. Statement of Robert J. Meyer, M.D. before the House Committee on Government Reform, September 13, 2005. 2005 [cited 2005 Mar 7]. Available from: http://www.fda.gov/NewsEvents/Testimony/ucm112718.htm

• **A complete overview of the different issues relating to the role of pharmacovigilance in identifying the potential of misuse of different prescribing molecules.**

7. Ator NA, Griffiths RR. Principles of drug abuse liability assessment in laboratory animals. Drug Alcohol Depend. 2003;70(Suppl 3):S55–S72.
8. Balster RL, Bigelow GE. Guidelines and methodological reviews concerning drug abuse liability assessment. Drug Alcohol Depend. 2003;70(Suppl 3):S13–S40.
9. Carter LP, Griffiths RR. Principles of laboratory assessment of drug abuse liability and implications for clinical development. Drug Alcohol Depend. 2009;105(Suppl 1):S14–S25.
10. Schwan S, Sundström A, Stjernberg E, et al. A signal for an abuse liability for pregabalin–results from the Swedish spontaneous

adverse drug reaction reporting system. Eur J Clin Pharmacol. 2010;66:947–953. doi:10.1007/s00228-010-0853-y.

• **In this study the Authors applied a Bayesian data-mining algorithm to reports of possible drug abuse or addiction in the Swedish national register of adverse drug reactions (SWEDIS), hence calculating the information component (IC) for pregabalin and reports of abuse and addiction.**

11. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). Guidance for Industry; E2E Pharmacovigilance Planning; April 2005 [cited 2016 Mar 7]. Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073107.pdf
12. Blanch B, Buckley NA, Mellish L, et al. Harmonizing post-market surveillance of prescription drug misuse: a systematic review of observational studies using routinely collected data (2000–2013). Drug Saf. 2015;38:553–564.
13. World Health Organization (WHO). 34th meeting of the WHO Expert Committee on Drug Dependence (ECDD); 2006 Mar 28–31; Geneva, Switzerland.
14. European Medicines Agency. Guideline on the use of statistical signal detection methods in the EudraVigilance data analysis system; 2008 [cited 2016 Mar 9]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011434.pdf
15. Hauben M, Madigan D, Gerrits CM, et al. The role of data mining in pharmacovigilance. Expert Opin Drug Saf. 2005;4:929–948.
16. Prieto-Merino D, Quartey G, Wang J, et al. Why a Bayesian approach to safety analysis in pharmacovigilance is important. Pharm Stat. 2011;10:554–559.
17. Micallef J, Frauger E, Palmaro A, et al. Example of an investigation of an "emergent" phenomenon in addiction vigilance: the case of methylphenidate. Therapie. 2015;7:191–202.
18. Evans-Brown M. Toxicovigilance of new psychoactive substances – perspectives from the EU Early Warning System. Toxicol Lett. 2015;238S:S2–S11.
19. Henningfield JE, Schuster CR. Risk management and post-marketing surveillance of CNS drugs. Drug Alcohol Depend. 2009;105(Suppl 1):S56–S64.
20. Deluca P, Davey Z, Corazza O, et al. Identifying emerging trends in recreational drug use; outcomes from the Psychonaut Web Mapping Project. Prog Neuropsychopharmacol Biol Psychiatry. 2012;39:221–226.

•• **This paper presents the outcomes of the 2-year European Union funded Psychonaut Web Mapping Project which aimed at developing and implementing an integrated web mapping system to promptly identify and learn about novel psychoactive substances (NPS; "legal highs") through the regular monitoring of the Internet.**

21. Siemann H, Specka M, Schifano F, et al. Salvia divinorum–representation of a new drug in the Internet. Gesundheitswesen. 2006;68:323–327.
22. Odgers DJ, Harpaz R, Callahan A, et al. Analyzing search behavior of healthcare professionals for drug safety surveillance. Pac Symp Biocomput. 2015;306–317.
23. Sarker A, Ginn R, Nikfarjam A, et al. Utilizing social media data for pharmacovigilance: A review. J Biomed Inform. 2015;54:202–212.
24. Eysenbach G. Infodemiology and infoveillance tracking online health information and cyberbehavior for public health. Am J Prev Med. 2011;40(5Suppl 2):S154–S158.
25. Kozinets RV. Netnography: understanding networked communication society. In: Quan-Haase A, Sloan L, editor. The SAGE handbook of social media research methods; 2016 [cited 2016 Mar 8]. Available from: https://www.researchgate.net/publication/280837429_Netnography_Understanding_Networked_Communication_Society_–a_first_draft_book_chapter_for_the_upcoming_volume_SAGE_Social_Media_Research_Methods
26. White RW, Harpaz R, Shah NH, et al. Toward enhanced pharmacovigilance using patient-generated data on the internet. Clin Pharmacol Ther. 2014;96(2):239–246.
27. Sarker A, O'Connor K, Ginn R, et al. Social media mining for toxicovigilance: automatic monitoring of prescription medication abuse from twitter. Drug Saf. 2016;39:231–240.

•• **A very innovative approach is presented here; the Authors carried out social media mining activities for toxicovigilance purposes just taking into account twitter entries.**

28. Sarker A, Ginn R, Nikfarjam A, et al. Utilizing social media data for pharmacovigilance: A review. J Biomed Inform. 2015;54:202–212.
29. Leiderman DB. Risk management of drug products and the U.S. Food and Drug Administration: evolution and context. Drug Alcohol Depend. 2009;105 Suppl 1:S9–S13.
30. Spillane J, McAllister WB. Keeping the lid on: a century of drug regulation and control. Drug Alcohol Depend. 2003;70(3 Suppl):S5–S12.
31. Reeves RR. Abuse of olanzapine by substance abusers. J Psychoactive Drugs. 2007;39(3):297–299.
32. Valeriani G, Corazza O, Bersani FS, et al. Olanzapine as the ideal "trip terminator"? Analysis of online reports relating to antipsychotics' use and misuse following occurrence of novel psychoactive substance-related psychotic symptoms. Hum Psychopharmacol. 2015;30:249–254. doi:10.1002/hup.2431.
33. Klein-Schwartz W, Schwartz EK, Anderson BD. Evaluation of quetiapine abuse and misuse reported to poison centers. J Addict Med. 2014;8:195–198.
34. Bogart GT, Ott CA. Abuse of second-generation antipsychotics: what prescribers need to know. Curr Psychiatr. 2011;10(5). [cited 2016 Mar 2]. Available from: http://www.currentpsychiatry.com/index.php?id=22661&tx_ttnews[tt_news]=176014
35. Malekshahi T, Tioleco N, Ahmed N, et al. Misuse of atypical antipsychotics in conjunction with alcohol and other drugs of abuse. J Subst Abuse Treat. 2015;48(1):8–12.
36. Francesconi G, Orsolini L, Papanti D, et al. Venlafaxine as the 'baby ecstasy'? Literature overview and analysis of web-based misusers' experiences. Hum Psychopharmacol. 2015;30(4):255–261. doi:10.1002/hup.2476.
37. Anand JS, Habrat B, Sut M, et al. Misuse of substances theoretically without abuse potential–case series. Przegl Lek. 2009;66(6):290–292.
38. Stahl SM. Essential psychopharmacology. Neuroscientific basis and practical applications. 4th ed. Cambridge: Cambridge University Press; 2013.
39. Bersani FS, Corazza O, Simonato P, et al. Drops of madness? Recreational misuse of tropicamide collyrium; early warning alerts from Russia and Italy. Gen Hosp Psychiatry. 2013;35:571–573.
40. Medicines.org.uk. Olanzapine medication package; 2016 [cited 2016 Mar 7]. Available from: https://www.medicines.org.uk/emc/PIL.30951.latest.pdf
41. Medicines.org.uk. Quetiapine medication package; 2016 [cited 2016 Mar 7]. Available from: https://www.medicines.org.uk/emc/PIL.26650.latest.pdf
42. Medicines.org.uk. Venlafaxine medication package; 2016 [cited 2016 Mar 7]. Available from: https://www.medicines.org.uk/emc/PIL.8609.latest.pdf
43. Medicines.org.uk. Tropicamide medication package; 2016 [cited 2016 Mar 7]. Available from: https://www.medicines.org.uk/emc/PIL.24751.latest.pdf
44. ACMD. ACMD advice on pregabalin and gabapentin; 2016 [cited 2016 Mar 7. Available from: https://www.gov.uk/government/publications/advice-on-the-anticonvulsant-drugs-pregabalin-and-gabapentin
45. Schifano F, D'Offizi S, Piccione M, et al. Is there a recreational misuse potential for pregabalin? Analysis of anecdotal online reports in comparison with related gabapentin and clonazepam data. Psychother Psychosom. 2011;80(2):118–122.
46. McNamara S, Stokes S, Kilduff R, et al. Pregabalin abuse amongst opioid substitution treatment patients. Ir Med J. 2015;108(10):309–310.
47. Canadian Agency for Drugs and Technologies in Health (CADTH). Abuse and misuse potential of pregabalin: a review of the clinical evidence; Context and policy issues; 2012 [cited 2016 Mar 7]. Available from: http://dpic.org/sites/default/files/PregabalinAbuse_CADTH_24Apr2012.pdf

48. Grosshans M, Mutschler J, Hermann D, et al. Pregabalin abuse, dependence, and withdrawal: a case report. Am J Psychiatry. 2010;167(7):869.
49. Cicero TJ, Ellis MS. Abuse-deterrent formulations and the prescription opioid abuse epidemic in the United States: lessons learned from oxycontin. JAMA Psychiatry. 2015;72(5):424–430.
50. Orsolini L, Francesconi G, Papanti D, et al. Profiling online recreational/prescription drugs' customers and overview of drug vending virtual marketplaces. Hum Psychopharmacol. 2015;30(4):302–318.
51. Orsolini L, Papanti GD, Francesconi G, et al. Mind navigators of chemicals' experimenters? A web-based description of e-psychonauts. Cyberpsychol Behav Soc Netw. 2015;18(5):296–300.
52. McColl S, Sellers EM. Research design strategies to evaluate the impact of formulations on abuse liability. Drug Alcohol Depend. 2006;83 Suppl 1:S52–S62.
53. Jack A. Can anyone stop the illegal sale of medicines online? BMJ. 2016;352:i1317.
54. Canadian Medical Association. CMA's Submission to the Senate Committee on Social Affairs, Science and Technology as part of its study on prescription pharmaceuticals: Federal levers to address unintended consequences of prescription pharmaceuticals and support public health, quality care, and patient safety; [cited 2016 Mar 7]. Available from: https://www.cma.ca/Assets/assets-library/document/en/advocacy/SOCI_BriefEnglish-Final.pdf