Research Paper

Adverse Drug Reactions at an Addiction Psychiatry Center: A Cross-sectional Analysis

Siddharth Sarkar, Rakesh K. Chadda, Anusha Thota[1], Naveen Kumar Dhagudu, Thota Prasad[1]

Department of Psychiatry and NDDTC, All India Institute of Medical Sciences, New Delhi, [1]Pharmacovigilance Programme of India, Indian Pharmacopoeia Commission (IPC), Ghaziabad, Uttar Pradesh, India

Abstract

Objective: To perform a cross sectional analysis of anticipated and unanticipated adverse drug reactions occurring at an addiction psychiatry center. **Materials and Methods:** This observational analysis presents data on the ADRs reported by the health-care professionals at a tertiary care public-funded treatment center. The types of ADRs encountered over a period of 12 months are presented along. **Results:** A total of 251 ADRs were encountered in patients with substance use disorders. Of them, 23% were unlabeled adverse reactions. At the center, tramadol was the most common medication implicated for ADR, followed by naltrexone and disulfiram. The most common adverse event reported was loss of appetite (n = 26). According to the system organ classification, gastrointestinal (18.7%) and psychiatric symptoms (18.7%) were the most common systems implicated. **Conclusion:** The current findings provide opportunities for sensitization of health-care professionals. This will help in promoting safer drug use in the field of addiction psychiatry.

Keywords: Causality assessment, National Drug Dependence Treatment Centre, pharmacovigilance, suspected adverse drug reaction

Introduction

Pharmacovigilance has an important role in assessment, monitoring, and discovery of effects of drugs in humans.[1,2] Pharmacovigilance activities continuously update the medical community about the adverse events associated with medications and inform clinical practice about the nature and severity of adverse drug reactions (ADRs).[3] This helps in rationalizing prescription patterns and clinical care and prevents harm from occurring in patients. Thus, it has been felt necessary to continue surveillance on medications, and mechanisms have been developed in an international framework to ascertain and compile ADRs.[4,5]

Continued monitoring of ADRs needs sustained efforts. This is particularly challenging in developing countries such as India which face issues of limited health-care services, large number of patients restricting the time spent on an individual patient, limited sensitization and practice of reporting ADRs, and lack of structured mechanisms of reporting.[6,7] The Pharmacovigilance Programme of India has been actively attempting to address these concerns and has setup ADR monitoring centers (AMCs) across the country to further the cause of reporting adverse effects with medications.[1] In general, the AMCs are based in multispecialty hospitals, and they report ADRs from diverse specialties.

Treatment of addictive disorders has gained prominence due to two factors: high prevalence of substance use disorders in the community and increasing recognition of substance use disorders as treatable conditions. Several pharmacological options are available for the treatment of substance use disorders.[8] Yet, the medications used for the management of substance use disorders can themselves be associated with some adverse effects. Reports of ADRs from an addiction treatment facility are thus likely to provide valuable information about the

Access this article online

Quick Response Code:

Website: www.jpharmacol.com

DOI: 10.4103/jpp.JPP_41_18

Address for correspondence: Siddharth Sarkar, Department of Psychiatry and NDDTC, Room No. 4096, Teaching Block, All India Institute of Medical Sciences, New Delhi - 110 029, India. E-mail: sidsarkar22@gmail.com

How to cite this article: Sarkar S, Chadda RK, Thota A, Dhagudu NK, Prasad T. Adverse drug reactions at an addiction psychiatry center: A cross-sectional analysis. J Pharmacol Pharmacother 2018;9:104-8.

Received: 31-03-2018 **Revised:** 31-05-2018 **Accepted:** 18-06-2018

medications' side effects among substance users. The National Drug Dependence Treatment Centre (NDDTC) of India is a specialized addiction treatment facility which is also an AMC of the Pharmacovigilance Programme of India. This helps the center to provide systematic data on side effects observed with medications used for the management of substance use disorders. We provide the data from the center which helps to put into context the anticipated and unanticipated adverse effects with medications used in the treatment of substance use disorders.

Materials and Methods

The present data were obtained from the NDDTC, the apex treatment center for substance use disorders in India. The NDDTC is a WHO collaboration center for substance abuse and has the mandate of clinical care, developing skilled workforce, conducting research, and providing policy directions. Patients with a variety of substance use disorders seek treatment at the NDDTC. This public-funded center has both outpatient and inpatient services. Patients with opioid, alcohol, or tobacco use disorders commonly seek treatment at the center. The center follows primarily a medical model of treatment. After the acute phase of detoxification, the maintenance treatment is started which is often prolonged. Medications are prescribed by trained physicians and dispensed by pharmacists. Many medications are provided free of cost from the center.

The present report is based on the routinely reported ADRs observed at the NDDTC from August 2016 to July 2017. The reporting was done by physicians, nurses, and pharmacists, and the reports were generated in the outpatient services as well as inpatient service. The reporting form is a standardized one as prescribed by the Pharmacovigilance Programme of India.[9] The reports do not contain the identifying information of the patients, and details about the adverse events observed and the medications are entered. The pharmacovigilance associate at the center compiles all the adverse drug reports and enters them in the Vigiflow system. Causality assessment was carried out using the WHO UMC causality assessment scale.[10]

Data analysis for the present report was done using SPSS version 21 (IBM Corp, Armonk, NY, USA). The data were collated, and descriptive statistics were used to represent the parameters such as gender, age, type of ADR, and the medication implicated. Further, whether the ADR was a labeled one (i.e., the package insert carrying information about the ADR) was also presented along with the causality assessment information. Missing value imputation was not done.

Results and Discussion

A total of 251 ADRs were recorded from August 2016 to July 2017 at the NDDTC. All the participants were males. The age distribution of the patients is presented in Figure 1. Table 1 presents the drugs implicated in the ADRs. The highest number of ADRs was reported for tramadol [97(38.6%)] followed by naltrexone (45 [17.9%]) and disulfiram (43 [17.1%]). Opioid dependence was the most common diagnosis for which the ADRs were reported.

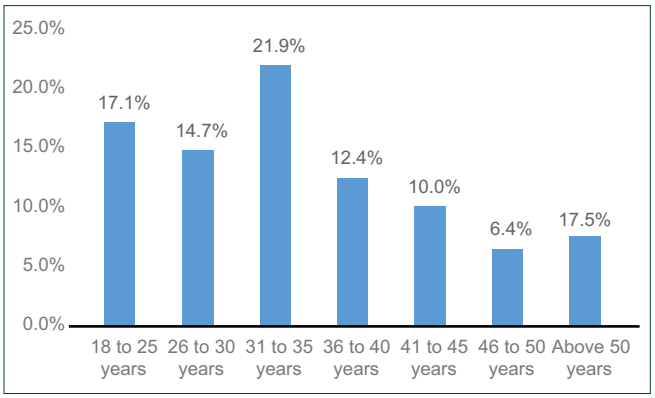

Figure 1: Age distribution of the sample

Table 1: Medications implicated in adverse drug reactions and their indications (*n* = 251)

	n (%)
Medication	
Tramadol	97 (38.6)
Naltrexone	45 (17.9)
Disulfiram	43 (17.1)
Buprenorphine	10 (4.0)
Multivitamins	10 (4.0)
Nitrazepam	8 (3.2)
Diazepam	7 (2.8)
Trazodone	6 (2.4)
Baclofen	6 (2.4)
Lorazepam	3 (1.2)
Others	13 (5.2)
Indications of use	
Opioid use disorder	156 (62.2)
Alcohol use disorder	77 (30.7)
Others	18 (7.2)

The types of ADRs and the organ systems implicated are presented in Tables 2 and 3, respectively. The most commonly reported ADR observed was appetite decrement in 26 (10.4%), followed by constipation in 15 (6.0%) and itching in 12 (4.8%). Tramadol was reported to cause the majority of ADRs. As per system organ classification, gastrointestinal system was the most affected organ system (*n* = 7, 18.7%), followed by psychiatric (*n* = 47, 18.7%), neurological (*n* = 39, 15.5%), and skin and appendage disorders 37 (14.7%).

The causality assessment is presented in Table 4. According to the WHO causality assessment scale, the most common ADRs were "possible" in 221 (88.0%). This was followed by "probable" in 19 (7.6%), "certain" in 9 (3.6%), and "unlikely" in 2 (0.8%). The reactions were classified as "nonserious" in 249 (99.2%). Most of the ADRs were nonserious in nature (*n* = 249, 99.2%) and only 2 (0.8%) were serious ADRs in the form of hospitalization or prolongation of the

Table 2: Common adverse drug reactions reported (*n* = 251)

Variable	*n* (%)
Appetite decreased	26 (10.4)
Constipation	15 (6.0)
Itching	12 (4.8)
Drug-alcohol interaction	10 (4.0)
Head fullness	10 (4.0)
Anxiety	7 (2.8)
Atonic seizures	7 (2.8)
Rash pruritic	7 (2.8)
Flushing	6 (2.4)
Headache	5 (2.0)
Rash	5 (2.0)
Weight increase	5 (2.0)
Diarrhea	4 (1.6)
Ejaculation premature	4 (1.6)
Epigastric discomfort	4 (1.6)
Eye pruritus	4 (1.6)
Stomach heaviness	4 (1.6)
Urinary hesitation	4 (1.6)
Vertigo	4 (1.6)
Vomiting	4 (1.6)
Weight decrease	4 (1.6)
Abdominal pain	3 (1.2)
Dizziness	3 (1.2)
Gastric irritation	3 (1.2)
Lacrimation abnormal	3 (1.2)
Lacrimation increased	3 (1.2)
Skin eruption	3 (1.2)
Others	82 (32.7)

Table 3: Adverse drug reactions according to the system organ classification (*n* = 251)

Variable	*n* (%)
Gastrointestinal	47 (18.7)
Psychiatric	47 (18.7)
Neurological	39 (15.5)
Skin and appendage	37 (14.7)
Vision	13 (5.2)
Urinary	12 (4.8)
Secondary terms	12 (4.8)
Metabolic nutritional	11 (4.4)
Body - general	7 (2.8)
Musculoskeletal	6 (2.4)
Vascular bleeding clotting	6 (2.4)
Reproductive	5 (2.0)
Immune	3 (1.2)
Cardiovascular	2 (0.8)
Hearing	2 (0.8)
Respiratory	2 (0.8)

hospital stay. About one in ten patients had recovered (*n* = 23, 9.2%), and 228 (81.8%) ADRs were classified as "unknown outcomes" due to lack of follow-up and definite information. About a fourth of the ADRs (*n* = 56, 22.3%) were not labeled, suggesting that these were either hitherto unreported or were so rare that they did not find mention in the package insert.

The present findings evaluate the suspected ADRs in a group of patients undergoing care at an addiction treatment facility. Specific group of patients enables more concerted and standard reporting of the adverse effects. Since management of substance use disorders requires long-term treatment, some of the ADRs are likely to be encountered after a period of time. The present report puts forth the types of ADRs seen in the context of treatment of substance use disorders. This is likely to be of relevance to patients, clinicians, and administrators. Such repository of information can be useful for capacity building for the treatment of substance use disorders.

One of the salient features has been the age distribution of the ADRs. The older age group was not overrepresented in the present report, which is at a variance from the previous studies.[11,12] This could be due to two reasons: the clientele of the center comprises primarily of substance using patients from lower age groups and the center does not take up patients who have medical problems as the primary focus of treatment. Hence, polypharmacy, which is common in patients in the elderly age group, is less commonly encountered at the center. The reports also comprised of patients of male gender only. This could be ascribed to the fact that females are underrepresented in India among the patients who seek treatment for substance use disorders.[13]

Out of 251 ADRs reports, tramadol, naltrexone, and disulfiram were the most common medications implicated. More than one-third of the ADRs were reported with tramadol. Currently, VigiAccess data reveal that there are >90,000 adverse drug reports with tramadol globally.[14] Asia is the largest contributor of the reported ADRs with tramadol. Gastrointestinal complaints, particularly, nausea, are the most common adverse effects of tramadol as per VigiAccess, similar to the present findings. The adverse events were generally nonserious in nature.

Among the organ systems, gastrointestinal system was the most commonly affected. The medications for treatment at the center were administered primarily by oral route, and hence, there was a greater possibility of gastrointestinal side effects. Previous literature also documents that gastrointestinal side effects were a common concern[15,16] though many large-scale pharmacovigilance reports suggest cutaneous adverse events to be the more commonly observed ones.[17,18] In addition, psychiatric symptoms such as anxiety, nervousness, and irritability were also common. The firm causal relationship was lacking in most of the circumstances because of the possibly alternative explanations for the observed symptoms (including features of substance withdrawal), hesitancy in dechallenge and rechallenge due to nonserious nature of the problems, and limited follow-up information. In causality assessment, the most common category endorsed was "possible." Literature from other general hospital settings also reveals that firm causality is difficult to be drawn in the routine clinical scenario.[15,19,20]

Table 4: Causality assessment, seriousness, outcome, and label status (*n* = 251)

	n (%)
Causality assessment	
Certain	9 (3.6)
Likely/probable	19 (7.6)
Possible	221 (88.0)
Unlikely	2 (0.8)
Seriousness	
Serious ADR	2 (0.8)
Nonserious	249 (99.2)
Outcome	
Recovered	23 (9.2)
Unknown	228 (90.8)
Label status	
Labeled	195 (77.7)
Not labeled	56 (22.3)

ADR=Adverse drug reaction

Although a majority of the adverse events encountered were labeled (i.e., the package inserts carrying information of these adverse events), many of the reported adverse events were nonlabeled. Reporting of both types of adverse events has their own significance. Labeled adverse events being reported means that the reporting is being carried out regularly. Nonlabeled adverse events being reported serves the purpose of pharmacovigilance by bringing to light the hitherto unknown side effects. The present report probably presents a healthy proportion of known and unknown side effects.

The results from the present report suggest that monitoring for adverse events during the course of treatment of patients with substance use disorders is important. Cognizance of the adverse events would be able to guide the clinical management better. Both expected and unexpected (nonlabeled) adverse events are likely to occur during the course of treatment. Cost-effective methods of reporting and disseminating the information are required in niche fields such as substance use disorders. Timely and efficient dissemination of information can help to empower the stakeholders in clinical care including the physicians, nurses, administrators, insurance providers, and the patients themselves.

Some limitations of the present report merit attention while interpreting the findings. The information was based on routine clinical care in a single center. Hence, generalizations to other contexts should be drawn with caution. The number of reports is limited, especially with regard to specific medications. This restricts the analysis, and hence, descriptive information is primarily presented. Further sophisticated statistical analysis can probably be done with larger samples. Furthermore, the follow-up information of the course of adverse events was selective and constrained. The inference of causality was largely "possible," given the real-world clinical setting. This limits the certainty of the association. Despite the limitations, the report presents the adverse event profile of a specific specialty of substance use disorders and is useful for informing clinical practice.

Conclusion

The present study presents information about ADRs among patients receiving treatment for substance use disorders. The health-care professionals need to be made more aware of ADRs, the importance of continued surveillance, and be stimulated for reporting. Further enquiries about the barriers in reporting, and the perceived benefits and cost analysis of an implemented program would be helpful in the advancement of the field. Vigilance about the adverse effects of medications is a collective responsibility for improving the outcome of clinical care.

Acknowledgments

Authors would like to acknowledge National Coordination Centre, Pharmacovigilance Programme of India, Indian Pharmacopoeia Commission, Ministry of Health and Family Welfare, Government of India, for their kind support.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Suke SG, Kosta P, Negi H. Role of pharmacovigilance in India: An overview. Online J Public Health Inform 2015;7:e223.
2. Amery WK, ISPE. Why there is a need for pharmacovigilance? Pharmacoepidemiol Drug Saf 1999;8:61-4.
3. Collaborating Centre for International Drug Monitoring, editor. The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products. Geneva: WHO; 2002.
4. Bate A, Lindquist M, Edwards IR. The application of knowledge discovery in databases to post-marketing drug safety: Example of the WHO database. Fundam Clin Pharmacol 2008;22:127-40.
5. Olsson S. The role of the WHO programme on international drug monitoring in coordinating worldwide drug safety efforts. Drug Saf 1998;19:1-10.
6. Olsson S, Pal SN, Stergachis A, Couper M. Pharmacovigilance activities in 55 low- and middle-income countries: A questionnaire-based analysis. Drug Saf 2010;33:689-703.
7. Olsson S, Pal SN, Dodoo A. Pharmacovigilance in resource-limited countries. Expert Rev Clin Pharmacol 2015;8:449-60.
8. Raby WN, Levin FR, Nunes EV. Psychiatry. In: Tasman A, Kay J, Lieberman JA, First MB, Maj M, editors. Pharmacological Treatment of Substance Abuse Disorders. West Sussex, England: John Wiley & Sons, Ltd.; 2008. p. 2390-416.
9. Thota A, Thota P, Kalaiselvan V, Sarkar S, Singh GN. Pharmacovigilance in drugs used in the treatment of drug dependence. Indian J Psychiatry 2017;59:393-5.
10. The Use of the WHO-UMC System for Standardized Case Causality Assessment. World Health Organization – Uppsala Monitoring Centre; 2018. Available from: https://www.who-umc.org/media/2768/standardised-case-causality-assessment.pdf. [Last accessed on 2018 May 31].
11. Patel TK, Patel PB. Incidence of adverse drug reactions in Indian hospitals: A systematic review of prospective studies. Curr Drug Saf 2016;11:128-36.
12. Kongkaew C, Noyce PR, Ashcroft DM. Hospital admissions associated with adverse drug reactions: A systematic review of prospective

observational studies. Ann Pharmacother 2008;42:1017-25.
13. Sarkar S, Balhara YP, Gautam N, Singh J. A retrospective chart review of treatment completers versus noncompleters among in-patients at a tertiary care drug dependence treatment centre in India. Indian J Psychol Med 2016;38:296-301.
14. Available from: http://www.vigiaccess.org/. [Last accessed on 2018 May 31].
15. Palaniappan M, Selvarajan S, George M, Subramaniyan G, Dkhar SA, Pillai AA, *et al*. Pattern of adverse drug reactions reported with cardiovascular drugs in a tertiary care teaching hospital. J Clin Diagn Res 2015;9:FC01-4.
16. Horen B, Montastruc JL, Lapeyre-Mestre M. Adverse drug reactions and off-label drug use in paediatric outpatients. Br J Clin Pharmacol 2002;54:665-70.
17. Shin YS, Lee YW, Choi YH, Park B, Jee YK, Choi SK, *et al.* Spontaneous reporting of adverse drug events by Korean regional pharmacovigilance centers. Pharmacoepidemiol Drug Saf 2009;18:910-5.
18. Marques J, Ribeiro-Vaz I, Pereira AC, Polónia J. A survey of spontaneous reporting of adverse drug reactions in 10 years of activity in a pharmacovigilance centre in Portugal. Int J Pharm Pract 2014;22:275-82.
19. Murphy BM, Frigo LC. Development, implementation, and results of a successful multidisciplinary adverse drug reaction reporting program in a university teaching hospital. Hosp Pharm 1993;28:1199-204, 1240.
20. Geer MI, Koul PA, Tanki SA, Shah MY. Frequency, types, severity, preventability and costs of adverse drug reactions at a tertiary care hospital. J Pharmacol Toxicol Methods 2016;81:323-34.