ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 17, Issue 4, 2024

Online - 2455-3891
Print - 0974-2441

Research Article

ADVERSE DRUG REACTIONS OF BACLOFEN, NALTREXONE, AND ACAMPROSATE IN PATIENTS HAVING ALCOHOL DEPENDENCE: A CROSS-SECTIONAL PHARMACOVIGILANCE STUDY

SUDHIR PANDURANG PANDHARE[1], DEVESH GOSAVI[1], KSHIROD KUMAR MISHRA[2], HARSHAL SHRIRAM SATHE[2]*

[1]Department of Pharmacology, Mahatma Gandhi Institute of Medical Sciences, Wardha, Maharashtra, India. [2]Department of Psychiatry, Mahatma Gandhi Institute of Medical Sciences, Wardha, Maharashtra, India.
***Corresponding author: Harshal Shriram Sathe; Email: harshals@mgims.ac.in**

Received: 03 November 2023, Revised and Accepted: 25 December 2023

ABSTRACT

Objectives: The research aims to investigate the prevalence and patterns of adverse drug reactions (ADRs), gauge the severity of these reactions, establish causality in ADR cases, and assess the preventability of such adverse reactions.

Methods: ADR information was gathered through personal interviews with patients or their relatives. Causality was assessed using the Naranjo algorithm, and a modified Hartwig and Siegel Severity Assessment Scale was used for estimating the severity of ADR. ADRs were grouped into various preventability categories based on the modified Schumock and Thornton criteria.

Results: The total number of patients evaluated in the baclofen, naltrexone, and acamprosate groups was 65, 28, and 42, respectively. The most commonly reported adverse events with baclofen were nausea (31.25%), followed by fatigue (18.75%) and headache (12.50%). The majority of patients receiving acamprosate reported nausea (57.14%), followed by diarrhea (28.57%). Patients receiving naltrexone most commonly reported nausea (35.71%), followed by abdominal pain (21.43%) and headache (14.28%).

Conclusion: This study shed light on the prevalence, severity, causality, and preventability of ADRs associated with anti-craving agents used to treat patients with alcohol withdrawal syndrome, providing valuable insights into the safety profiles of these medications.

Keywords: Pharmacovigilance, Anticraving drugs, Adverse drug reactions, Safety profile.

 DOI: http://dx.doi.org/10.22159/ajpcr.2024v17i4.49791. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Alcohol consumption ranks as the world's third-largest risk factor for disease and disability, with far-reaching socio-economic consequences such as child neglect, abuse, workplace absenteeism, and violence [1]. In response, researchers have endeavored to counteract the pleasurable effects of alcohol by developing anticraving medications that act on specific neurotransmitters [2]. The FDA-approved medications for treating alcohol use disorders include disulfiram, acamprosate, and naltrexone [3].

The Pharmacovigilance Program of India was launched by the Government of India on July 14, 2010, with the All India Institute of Medical Sciences in New Delhi as the National Coordination Centre, focusing on monitoring adverse drug reactions (ADRs) to safeguard public health [4]. The World Health Organization defines ADRs as harmful and unintended responses to drugs, occurring at normal therapeutic doses [5]. ADRs stand among the leading causes of morbidity and mortality, leading to hospitalizations and treatment non-compliance, often initiating medication discontinuation [5,6]. Despite the importance of ADR monitoring, health-care professionals lack awareness due to several reasons, such as the perceived commonality of ADRs, uncertainty regarding causality, limited knowledge of reporting procedures, a general lack of awareness, and the fear of legal ramification [7,8].

Baclofen, a centrally acting muscle relaxant belonging to the GABA mimetic drug group, selectively targets GABA receptors [9]. It shows promise as an anti-craving agent for alcoholism, but common side effects include significant fatigue, sleepiness, insomnia, dizziness, paresthesia, nausea, vomiting, and less frequently, sensory changes and sexual alterations, including changes in libido, as well as various forms of pain, including headaches [9]. Naltrexone, an opioid antagonist, is thought to reduce the desire to drink by blocking the pleasurable "high" effects of alcohol [9]. Early treatment may lead to gastrointestinal adverse events (AEs), including nausea, vomiting, and abdominal discomfort, as well as headaches and fatigue. In addition, hepatotoxicity has been reported, primarily in obese patients receiving high daily doses (100–300 mg), which can lead to immediate and severe withdrawal in opiate-dependent patients [10,11]. Acamprosate, functioning as an N-Methyl D-aspartate receptor antagonist with modest GABA receptor agonistic activity, is now the most widely prescribed therapeutic agent for alcoholism in the United States. It is generally well-tolerated, with no reported deaths or drug-related AEs. Diarrhea is the most common reason for discontinuation [9,12].

Given the increasing use of anti-craving agents, it is imperative to assess their safety profile. However, there are only a limited number of controlled clinical trials available on these drugs, indicating the need for larger studies in diverse treatment settings. Data on the safety of anti-craving agents in India, particularly in the central region, is scarce. Therefore, our study objectives center around the monitoring of ADRs associated with anti-craving agents prescribed within the Department of Psychiatry at a tertiary care teaching hospital in central India. The research aims to investigate the prevalence and patterns of ADRs, gauge the severity of these reactions, establish causality in ADR cases, and assess the preventability of such adverse reactions.

METHODS

Study settings and study population

The present research employed a cross-sectional and observational design. It was conducted at the psychiatry outpatient department

of a rural tertiary healthcare center and teaching hospital in central India over 18-month duration (from January 2019 to June 2020). The study included adult patients aged 18–60 years, diagnosed with alcohol dependence according to the tenth version of the International Classification of Diseases, and who had been taking at least one of the anticraving agents (baclofen, acamprosate, or naltrexone) for a minimum period of 1 month. These patients constituted the study population and were invited to participate after providing written informed consent. Exclusion criteria encompassed concurrent prescription of other psychotropic agents, the presence of psychiatric or medical co-morbidities, and unwillingness to participate in the study.

Data collection

The author visited the Psychiatry Outpatient Department on 2 days (Tuesday and Thursday) every week and collected data from all eligible patients seeking consultation and meeting the inclusion and exclusion criteria. Data were collected electronically using a pre-designed case record form (CRF) in Google Forms software. This form recorded patient demographics, including patient number, initials, age, sex, date, diagnosis, relevant investigations (if any), and routine physical examination findings. Detailed information on presenting symptoms, other medical and surgical illnesses, medication details (including drug or combination of drugs, start date, dose, route of administration, frequency, and co-medications), and patterns of ADRs were collected and documented in the CRF. ADR information was gathered through personal interviews with patients or their relatives. Details of ADRs present at the time of follow-up visits or those occurring between follow-up visits were recorded in the ADR reporting form.

Assessment of causality

Causality was assessed using the Naranjo algorithm [13], a 10-item clinician-rated questionnaire that evaluates the causal relationship between ADRs and the medications being used. Each item had responses of "yes," "no," or "don't know" and was assigned a numerical score based on the manual. Causality was then classified as definite (9 or more), probable (5–8), possible (1–4), or doubtful (0) based on the total score generated.

Assessment of severity

Reported ADRs were categorized into various severity levels based on the Modified Hartwig and Siegel severity assessment scale [14], which includes seven levels from ADRs requiring no modification in drug administration (Level 1) to ADRs directly or indirectly leading to death (Level 7). These ADR levels were further grouped into mild (Levels 1 and 2), moderate (Levels 3 and 4), and severe (Levels 5–7) categories based on responses.

Assessment of preventability

Reported ADRs were grouped into various preventability categories based on the modified Schumock and Thornton criteria [15]. This scale was used to determine the preventability of ADRs, categorizing them as definitely preventable, probably preventable, or not preventable.

Ethical considerations

The investigators commenced the study after obtaining approval from the Institutional Ethics Committee. Written informed consent was taken from all the participants in the local language. In the event of any difficulties, a senior psychiatrist was available for consultation. All decisions related to patient management, including medications and investigations, were made by the treating psychiatrist. The investigator did not interfere in patient management but solely observed the proceedings and recorded the findings.

Table 1: Frequency of ADR in patients

Adverse events	Baclofen (%)	Naltrexone (%)	Acamprosate (%)
Present	16 (24.62)	14 (50)	7 (16.67)
Absent	49 (75.38)	14 (50)	35 (83.33)
Total	65 (100)	28 (100)	42 (100)

Table 2: System-wise distribution of ADR

System	ADR	Baclofen (n=65)	Naltrexone (n=28)	Acamprosate (n=42)	Total (n=135) n (%)	Total system-wise ADR (n=135) n (%)
Gastrointestinal tract	Nausea	5 (20)	5 (20)	4 (16)	14 (56)	25 (67.57)
	Abdominal Pain	1 (4)	3	1 (4)	5 (20)	
	Vomiting	1 (4)	1 (4)	0 (0)	2 (8)	
	Diarrhea	0 (0)	0 (0)	2 (8)	2 (8)	
	Constipation	1 (4)	0 (0)	0 (0)	1 (4)	
	Abdominal discomfort	0 (0)	1 (4)	0 (0)	1 (4)	
Central Nervous System	Headache	2 (28.5)	2 (28.5)	0 (0)	4 (57.14)	7 (18.92)
	Insomnia	1 (14.28)	0 (0)	0 (0)	1 (14.28)	
	Dizziness	1 (14.28)	0 (0)	0 (0)	1 (14.28)	
	Mental Confusion	1 (14.28)	0 (0)	0 (0)	1 (14.28)	
Others	Fatigue	3 (60)	1 (20)	0 (0)	4 (80)	5 (13.51)
	Restlessness	0	1 (20)	0 (0)	1 (20)	

Table 3: Causality, severity, and preventability of ADR in patients on anticraving drugs

Categories	Baclofen	Naltrexone	Acamprosate	Total n (%)
Causality categories (Naranjo algorithm)				
Definite	0 (0)	0 (0)	0 (0)	0 (0)
Probable	14 (37.8)	10 (27.02)	7 (18.9)	31 (83.78)
Possible	2 (5.4)	4 (10.8)	0 (0)	6 (16.22)
Doubtful	0 (0)	0 (0)	0 (0)	0 (0)
Severity categories (Seigal–Hartwig scale)				
Mild	14 (37.8)	8 (21.6)	7 (18.9)	29 (78.38)
Moderate	2 (5.4)	4 (10.8)	0 (0)	8 (21.62)
Severe	0 (0)	0 (0)	0 (0)	0 (0)
Preventability categories (Modified Schumock Thorton criteria)				
Not Preventable	14 (37.8)	11 (29.7)	5 (13.5)	30 (78.38)
Probably preventable	2 (5.4)	3 (8.1)	2 (5.4)	7 (21.62)
Definitely preventable	0 (0)	0 (0)	0 (0)	0 (0)

Statistical analysis

Data were tabulated and cleaned using Microsoft Excel software and subsequently transferred to Epi Info software version 7 for statistical analysis [16]. Descriptive statistics were used to present the number of ADRs categorized by system and according to the different anti-craving agents used, presented as frequencies and percentages.

RESULTS

Our study compared AEs among patients with alcohol dependence who were taking anti-craving drugs. The total number of patients evaluated in the baclofen, naltrexone, and acamprosate groups was 65, 28, and 42, respectively (The frequency of ADRs in patients shown in Table 1). The most commonly reported AEs with baclofen were nausea (31.25%), followed by fatigue (18.75%) and headache (12.50%). The majority of patients receiving acamprosate reported nausea (57.14%), followed by diarrhea (28.57%). Patients receiving naltrexone most commonly reported nausea (35.71%), followed by abdominal pain (21.43%) and headache (14.28%) (Findings given in Table 2).

According to the Naranjo algorithm, the majority of the AEs (83.78%) were categorized as probable, with only 16.22% falling into the possible category. Among the 31 probable AEs, 7 were associated with acamprosate, 10 with naltrexone, and 14 with baclofen. The Hartwig–Siegel scale score analysis showed that the majority of the AEs (78.38%) were of mild severity, while 21.62% were of moderate severity. Naltrexone (6) and baclofen (2) accounted for most of the moderate AEs. There were no severe AEs associated with any of the anti-craving agents. The modified Schumock and Thornton criteria, used to assess preventability, showed that the majority of the AEs were not preventable (81.08%), while only 18.92% were probably preventable. Among the 30 not-preventable AEs, 5 were observed with acamprosate, 11 with naltrexone, and 14 with baclofen (The causality, severity and preventability of ADRs in patients shown in Table 3).

DISCUSSION

In an observational, cross-sectional study conducted over an 18-month period, the primary objective was to monitor ADRs associated with anti-craving agents prescribed to patients attending the department of psychiatry at a tertiary care teaching institute situated in Central India. Throughout this study, each patient diagnosed with alcohol withdrawal syndrome received one of three different anti-craving agents. Thus, 65, 28, and 42 patients were evaluated for ADRs in the baclofen, naltrexone, and acamprosate groups, respectively.

Notably, the study revealed that the highest occurrence of ADRs was among patients receiving naltrexone, with 50% reporting AEs. Baclofen and acamprosate exhibited lower incidence rates, with 24.62% and 16.67% of patients reporting ADRs, respectively. Therefore, among the three anti-craving agents, acamprosate demonstrated the highest tolerance. Nevertheless, it is worth mentioning that a study by Kumar *et al*. suggested that Baclofen had the best tolerance with the fewest ADRs. Among the patients receiving naltrexone, the majority (40%) experienced ADRs, followed by those receiving acamprosate (26.66%) and baclofen (16.66%) [17]. Discrepancies in these findings can be attributed to differences in study settings and sampling methodologies. The study also pinpointed the most commonly reported ADRs associated with each anti-craving agent. For baclofen, nausea (31.25%) ranked the highest, followed by fatigue (18.75%) and headache (12.50%). It is noteworthy that fatigue, sleep disorders, and vertigo/dizziness were frequently reported ADRs, particularly in high-dose studies, and reports of more severe ADRs such as major sedation, seizures, mania, and sleep apnea have been increasing in line with expanded usage [18]. For patients receiving acamprosate, the majority reported nausea (57.14%), followed by diarrhea (28.57%). Interestingly, another study suggested that acamprosate is generally well-tolerated, with limited side effects, primarily transient diarrhea (10%) and headache (20%) [19]. Additional common complaints among acamprosate recipients included increased appetite (11.1%), decreased libido (8.3%), sleep disturbances (8.3%), joint or muscle pain (8.3%), and memory impairment (6.9%) [20]. Finally, the majority of patients receiving naltrexone reported nausea (35.71%), followed by abdominal pain (21.43%) and headache (14.28%). According to Pettinati *et al*., nausea and vomiting are the most frequently reported side effects with naltrexone, while headache, low energy, anxiety, depression, rashes, and decreased alertness are less common [21,22].

Regarding causality, the study showed that the majority of ADRs were categorized as "probable" (83.78%), with only 16.22% falling into the "possible" category. Reynaud *et al*. reported that 46% of ADRs associated with baclofen were deemed unrelated to the study treatment by the investigators [23]. In a similar vein, Soyka *et al*. noted that out of nine serious ADRs, only two were tentatively linked to acamprosate, namely, diarrhea and dermatitis [24]. In terms of ADR severity, the majority were classified as "mild" (78.38%), with "moderate" ADRs accounting for only 21.62%. Similarly, Reynaud *et al*. reported that the majority of AEs associated with Baclofen were of mild intensity (59.8%), with a substantial portion categorized as moderate (31.6%).[23] On the other hand, Mason *et al*. found that the co-administration of acamprosate and naltrexone yielded no severe AEs, and 94% of all AEs were classified as mild in terms of severity [24]. However, Soyka *et al*. reported that a small percentage of patients (1.0%) discontinued acamprosate treatment due to serious AEs. When it came to preventability, most ADRs were considered "not preventable" (81.08%), with only 18.92% deemed "probably preventable."

It is important to note that the study faced certain limitations. For instance, in causality assessment, re-challenge tests were required for definitive conclusions, but ethical constraints prevented their execution. In addition, laboratory investigations were not conducted during the study, which meant that ADRs identifiable through laboratory findings could not be identified or studied.

CONCLUSION

In summary, this study shed light on the prevalence, severity, causality, and preventability of ADRs associated with anti-craving agents used to treat patients with alcohol withdrawal syndrome, providing valuable insights into the safety profiles of these medications.

AUTHOR CONTRIBUTIONS

All the contributors to the manuscript have been given authorship as per ICMJE guidelines.

CONFLICTS OF INTEREST

None.

FUNDING

None.

REFERENCES

1. Patterns and Consequences of alcohol Misuse in India-an Epidemiological Survey. Karnataka: National Institute of Mental Health and Neurosciences (NIMHANS); 2011.
2. Fuller RK, Hiller-Sturmhöfel S. Alcoholism treatment in the United States. An overview. Alcohol Res Health. 1999;23(2):69-77. PMID 10890799
3. Akbar M, Egli M, Cho YE, Song BJ, Noronha A. Medications for alcohol use disorders: An overview. Pharmacol Ther. 2018 May 1;185:64-85. doi: 10.1016/j.pharmthera.2017.11.007, PMID 29191394
4. Kalaiselvan V, Thota P, Singh GN, Pharmacovigilance programme of India. Pharmacovigilance Programme of India: Recent developments and future perspectives. Indian J Pharmacol. 2016 Nov-Dec;48(6):624-8. doi: 10.4103/0253-7613.194855, PMID 28066097
5. Olsson S, Parthasarathi G. Adverse drug reactions and pharmacovigilance. A Textbook of Clinical Pharmacy Practice: Essential nd Concepts and Skills. 2012;2:117-8.
6. Akici A, Oktay S. Rational pharmacotherapy and pharmacovigilance. Curr Drug Saf. 2007;2(1):65-9. doi: 10.2174/157488607779315408, PMID 18690951

7. Tandon VR, Mahajan V, Khajuria V, Gillani Z. Under-reporting of adverse drug reactions: A challenge for pharmacovigilance in India. Indian J Pharmacol. 2015;47(1):65-71. doi: 10.4103/0253-7613.150344.
8. Lucca JM, Madhan R, Gurumurthy P, Dushad R. A prospective observational study to evaluate safety reporting of antidepressants at a tertiary care hospital in India. Indian J Pharmacol. 2014;46(5):543-6. doi: 10.4103/0253-7613.140591, PMID 25298586
9. Tripathi KD. Essentials of Medical Pharmacology. 8th ed. New Delhi: Jaypee Brothers Company. p. 384.
10. Latt NC, Jurd S, Houseman J, Wutzke SE. Naltrexone in alcohol dependence: A randomised controlled trial of effectiveness in a standard clinical setting. MJA. Med J Aust. 2002;176(11):530-4. doi: 10.5694/j.1326-5377.2002.tb04550.x, PMID 12064984
11. Anton RF. Naltrexone for the management of alcohol dependence. N Engl J Med. 2008;359(7):715-21. doi: 10.1056/NEJMct0801733, PMID 18703474
12. Mason BJ, Heyser CJ. Acamprosate: A prototypic neuromodulator in the treatment of alcohol dependence. CNS Neurol Disord Drug Targets. 2010;9(1):23-32. doi: 10.2174/187152710790966641, PMID 20201812
13. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al*. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981 Aug;30(2):239-45. doi: 10.1038/clpt.1981.154, PMID 7249508
14. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm. 1992 Sep 1;49(9):2229-32. doi: 10.1093/ajhp/49.9.2229, PMID 1524068
15. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm. 1992;27(6):538. PMID 10118597
16. Dean AG, Arner TG, Sunki GG, Friedman R, Lantinga M, Sangam S, *et al*. Epi Info™, a Database and Statistics Program for Public Health Professionals. Atlanta: Centers for Disease Control and Prevention (US); 2011.
17. Kumar A, Sharma A, Bansal PD, Bahetra M, Gill HK, Kumar R. A comparative study on the safety and efficacy of naltrexone versus Baclofen versus acamprosate in the management of alcohol dependence. Indian J Psychiatry. 2020;62(6):650-8. doi: 10.4103/psychiatry.IndianJPsychiatry_201_19, PMID 33896969
18. Goh ET, Morgan MY. Review article: Pharmacotherapy for alcohol dependence-the why, the what and the wherefore. Aliment Pharmacol Ther. 2017;45(7):865-82. doi: 10.1111/apt.13965, PMID 28220511
19. Jung YC, Namkoong K. Pharmacotherapy for alcohol dependence: Anticraving medications for relapse prevention. Yonsei Med J. 2006;47(2):167-78. doi: 10.3349/ymj.2006.47.2.167, PMID 16642544
20. Namkoong K, Lee BO, Lee PG, Choi MJ, Lee E. Acamprosate in Korean alcohol-dependent patients: A multi-centre, randomized, double-blind, placebo-controlled study. Alcohol Alcohol. 2003;38(2):135-41. doi: 10.1093/alcalc/agg038, PMID 12634260
21. Pettinati HM, O'Brien CP, Rabinowitz AR, Wortman SP, Oslin DW, Kampman KM, *et al*. The status of naltrexone in the treatment of alcohol dependence: Specific effects on heavy drinking. J Clin Psychopharmacol. 2006;26(6):610-25. doi: 10.1097/01.jcp.0000245566.52401.20, PMID 17110818
22. Garbutt JC. Efficacy and tolerability of naltrexone in the management of alcohol dependence. Curr Pharm Des. 2010;16(19):2091-7. doi: 10.2174/138161210791516459, PMID 20482515
23. Reynaud M, Aubin HJ, Trinquet F, Zakine B, Dano C, Dematteis M, *et al*. A randomized, placebo-controlled study of high-dose Baclofen in alcohol-dependent patients-the ALPADIR study. Alcohol Alcohol. 2017;52(4):439-46. doi: 10.1093/alcalc/agx030, PMID 28525555
24. Soyka M, Preuss U, Schuetz C. Use of acamprosate and different kinds of psychosocial support in relapse prevention of alcoholism. Results from a non-blind, multicentre study. Drugs R D. 2002;3(1):1-12. doi: 10.2165/00126839-200203010-00001, PMID 11881521