

Benzodiazepine resistant alcohol withdrawal: What is the clinician's preferred definition?

Hugo Langlois ¹, PharmD, MSc*; Monique Cormier[†]; Eric Villeneuve ², PharmD, MSc*; Robert S. Hoffman, MD^{†‡}; Cristina Longo, PhD[§]; Sophie Gosselin ¹, MD^{†¶**}

CLINICIAN'S CAPSULE

What is known about the topic?

Benzodiazepine-resistant alcohol withdrawal syndrome is not well defined in the literature.

What did this study ask?

We assessed clinicians' personal definition of resistant alcohol withdrawal with a survey-based approach.

What did this study find?

High benzodiazepine dosage (40 mg/hr of diazepam equivalents) was considered a determinant for defining resistant alcohol withdrawal.

Why does this study matter to clinicians?

High benzodiazepine usage should prompt clinicians to suspect resistant alcohol withdrawal syndrome and add another molecule such as phenobarbital.

withdrawal as a high benzodiazepine dosage. Seizures (26%) and persistent tachycardia (16%) were also main characteristics. The median dose to describe high benzodiazepine dose (n = 146) was 40 mg per hour of diazepam equivalents (IQR 20–50). Available definitions were ranked equally as the preferred one: Hack (27%); Benedict (28%); Hughes (28%).

Conclusion: Our results did not identify one single preferred definition for resistant alcohol withdrawal even though a high total dose of benzodiazepine is a major component. Hourly requirements of 40 mg of diazepam equivalents or more emerged as a possible threshold. These findings serve as a base to explore consensus guidelines or future research.

RÉSUMÉ

Objectif: Si le syndrome de sevrage à l'alcool est un trouble fréquent, la reconnaissance du syndrome de sevrage à l'alcool résistant aux benzodiazépines est relativement nouvelle. Afin de fournir un cadre de travail se prêtant aussi bien aux revues de la documentation qu'aux recherches futures, l'équipe a évalué les définitions personnelles que les cliniciens ont du syndrome de sevrage à l'alcool résistant aux benzodiazépines.

Méthode: Nous avons développé une étude transversale par les biais d'un sondage électronique. Les administrateurs des associations participantes en toxicologie et en médecine d'urgence ont mis directement le questionnaire à la disposition de leurs membres respectifs. Seuls les médecins, les pharmaciens et d'autres cliniciens habitués au traitement du syndrome de sevrage à l'alcool pouvaient participer à l'étude. Les répondants devaient choisir, parmi les trois définitions les plus courantes du syndrome de sevrage à l'alcool résistant aux benzodiazépines (Hack, Benedict, Hughes), celle qu'ils préféraient, ou encore donner leur propre définition. D'autres critères visant à définir le syndrome de sevrage à l'alcool résistant ont aussi été examinés.

Résultats: Au total, 384 personnes ont répondu au questionnaire. Il s'agissait, pour la plupart, de médecins traitants (79%), pratiquant à temps complet (90%), en médecine d'urgence (70%) et en Amérique du Nord (90%). La majorité (64%) d'entre

ABSTRACT

Objectives: Although alcohol withdrawal is common, the recognition of benzodiazepine-resistant alcohol withdrawal is a relatively new concept. To provide a framework for both literature review and future research, we assessed clinicians' personal definition of resistant alcohol withdrawal.

Method: We developed a cross-sectional web-based survey. Administrators from collaborating toxicology and emergency medicine associations deployed the survey directly to their respective memberships. Only physicians, pharmacists, and other clinicians routinely treating alcohol withdrawal were eligible to participate. Respondents selected their preferred definition among the three most common author sources – JB Hack, NJ Benedict, D Hughes – or provided their own. Additional criteria to define resistant alcohol withdrawal were explored.

Results: 384 individuals answered the survey. Respondents were mostly attending physicians (79%), in full-time practice (90%), in emergency medicine (70%), and from North America (90%). The majority (64%) described resistant alcohol

From the *Pharmacy Department, McGill University Health Centre, Montreal, QC; †Montreal Medical Toxicology Initiative, Montreal, QC; ‡Division of Medical Toxicology, Ronald O. Perelman Department of Emergency Medicine, New York University School of Medicine, NY; §Department of Family Medicine, McGill University, Montreal, QC; ¶Department of Emergency Medicine, McGill University Health Centre, Montreal, QC; and **Centre antipoison du Québec, Quebec City, QC.

Correspondence to: Hugo Langlois, 1001 Decarie Blvd., Montreal, QC H4A 3J1; Email: hugo.langlois.1@umontreal.ca

eux considérait le syndrome de sevrage à l'alcool comme résistant s'il nécessitait de fortes doses de benzodiazépines. La présence de convulsions (26%) et une tachycardie persistante (16%) figuraient aussi parmi les principales caractéristiques. La dose médiane de benzodiazépines considérée comme forte (n = 146) s'élevait à 40 mg en équivalent de diazépam, toutes les heures (intervalle interquartile : 20–50). Les définitions proposées ont recueilli un taux quasi égal de réponse, soit 27% pour Hack, 28% pour Benedict et 28% pour Hugues.

Conclusion: Les résultats de l'étude n'ont pas permis de dégager une seule définition du syndrome de sevrage à

l'alcool résistant, mais une dose totale élevée de benzodiazépines est considérée comme un élément important. Par ailleurs, des doses totales de 40 mg ou plus en équivalent de diazépam administrées toutes les heures pourraient marquer un seuil possible. Enfin, les résultats obtenus servent de fondements potentiels à l'élaboration de lignes directrices consensuelles et à de futurs travaux de recherche.

Keywords: Drugs and pharmacology, emergency medicine, resistant alcohol withdrawal, toxicology

INTRODUCTION

Alcohol withdrawal is a common problem in emergency departments.^{1,2} Although benzodiazepines are the first-line treatment,^{3,4} some withdrawal patients are poorly responsive to benzodiazepines. This entity is often named *benzodiazepine-resistant* or *resistant alcohol withdrawal*. Unfortunately, there is no standard definition of resistant alcohol withdrawal. Hack et al. suggested a combination of abnormal vital signs and a cumulative dose of more than 200 mg of diazepam over 3 hours.⁵ However, these criteria were never validated or subjected to expert consensus. Also, the definition of abnormal vital signs was imprecise. All subsequent definitions of resistant alcohol withdrawal seem to be variations on Hack's initial efforts. Among these, one suggests that more than 10 mg of lorazepam in 1 hour or more than 40 mg in 4 hours would define benzodiazepine resistance.⁶ A recent retrospective study defined benzodiazepine resistance based on three different criteria: 200 mg of diazepam in 4 hours; greater than 40 mg of diazepam in 1 hour; or an individual dose of greater than 40 mg of diazepam required to control agitation.⁷ A formalized definition of resistant withdrawal might standardize future research by improving comparability of patients, which ultimately could improve the assessment of interventions on relevant clinical outcomes. The present study assesses clinicians' personal definitions of resistant alcohol withdrawal with a survey-based methodology.

METHODS

Study design and population

We designed a 25-item open cross-sectional survey assessing two different aspects of alcohol withdrawal

among emergency physicians and toxicologists. The first part assesses clinicians' personal definition of resistant alcohol withdrawal. The questionnaire was imported on the SimpleSurvey platform, a web-based online survey tool. It was displayed on three pages; the first was the consent form, and the others were 13- and 12-item questionnaires, respectively. The survey link was available from July 5, 2017, to September 18, 2017. A convenience sample of associations was based on their willingness and costs to deploy the survey.

The administrators of the Canadian Association of Emergency Physicians (n = 1,447), the European Association of Poison Centres and Clinical Toxicologists (n = 291), the American Academy of Clinical Toxicologists (n = 504), the Asian Pacific Association of Medical Toxicologist (n = 344), the American College of Medical Toxicology (n = 680), and the Association des Pharmaciens d'Établissements de Santé of Quebec (n = 1,978) sent a survey link to their membership. A single reminder was sent 2 weeks before closing the survey. Participation was voluntary. Due to known cross-memberships, eligible respondents were asked to complete the survey once only. Only physicians, pharmacists, or other clinicians managing alcohol withdrawal were eligible to participate. Informed consent was obtained at the beginning of the survey. Answers were anonymous. Ten minutes was the estimated time to complete the survey. This study was approved by our institutional Research and Ethics Board. The CHERRIES checklist was used to report the results.⁸

Survey design

The questionnaire's content was based on a literature review performed by local experts with backgrounds in clinical research and toxicology. The questionnaire

was developed in English and French and was piloted among five local emergency physicians. Written feedback was requested and received by email. Respondents were asked to rank from 1 to 3, three literature-based definitions of resistant alcohol withdrawal, with choice 1 being their preference. Respondents were required to comment on whether they considered these definitions equivalent. Additionally, they could specify their own criteria for resistant alcohol withdrawal. Answers could be reviewed and changed using the “Back” button at any time before submitting their questionnaire. The survey questions are in supplementary material Appendix 1.

Data analysis

All answers were collected with the SimpleSurvey platform and extracted on an Excel spreadsheet (Microsoft Corp, Redmond, WA). An independent statistician eliminated duplicates by comparing IP addresses and demographics; only identical matches were deleted. We summarized categorical responses with counts and proportions. Median and interquartile ranges (IQRs) were calculated for the continuous responses. Benzodiazepine equivalence was defined as diazepam 5 mg = lorazepam 1 mg to express diazepam dosing equivalents (DEQ).⁹ Statistical analyses were performed with R studio version 1.1.447 (RStudio, Inc., Boston, MA). The response rate could not be accurately estimated because an unknown proportion of recipients received more than one invitation due to overlap in membership/ mailing lists. We therefore defined the participation rate as the proportion of respondents who agreed to participate divided by the number of times the survey link was opened. Surveys that were not completed for at least one question were excluded.

RESULTS

Respondent characteristics

The response rate was 8.6% (453/5244), the participation rate was 48.5% (453/934), and the completion rate was 70.4% (319/453). Respondents totalling 384 provided adequate data for analysis; 302 (78.6%) were attending physicians, 344 (89.6%) had a full-time practice, and 270 (70.3%) were practising emergency medicine. Most respondents (73.7%) were practising for less than 20 years, and 223 respondents (58.1%) treated

Table 1. Definitions of resistant alcohol withdrawal

Hack ⁵	Abnormal vital signs and a total dose of >200 mg of diazepam over 3 hours
Benedict ⁶	One of the three different criteria: 1) >200 mg of diazepam in 4 hours 2) >40 mg of diazepam in 1 hour 3) An individual dose of >40 mg of diazepam to control agitation
Hughes ⁷	>10 mg of lorazepam in 1 hour or >40 mg in 4 hours

alcohol withdrawal patients at least once per week. Full respondent characteristics are shown in the supplementary material, Appendix Table 1.

Resistant alcohol withdrawal definition

Table 1 shows the literature-based definitions. Our survey used Benedict’s definition as included in the research protocol available on www.clinicaltrial.gov, which was different in the final publications.¹⁰ We referred to it as the protocol number definition in the survey. Resistant alcohol withdrawal was described as a high benzodiazepine dosage (i.e., diazepam 40 mg in 2 hours) by 244 respondents (63.5%) followed by seizures by 98 respondents (25.5%). These criteria were not mutually exclusive. Among the 146 respondents who quantified “high-dose benzodiazepine,” the median dose was 40 mg per hour (IQR; 20–50) of DEQ. See Table 2 for the full distribution of criteria surveyed.

The number of clinicians who ranked the three literature-based, resistant alcohol withdrawal definitions

Table 2. Distribution of criteria defining resistant alcohol withdrawal

Criteria suggested*	Response rate n (%)
High benzodiazepine dosage (i.e., 40 mg of diazepam over 2 hours)	244 (63.5)
Seizures	98 (25.5)
Persistent tachycardia	62 (16.1)
High score on evaluation tool	54 (14.1)
No definition [†]	10 (2.6)
Not commonly seen in practice [‡]	10 (2.6)
Agitation or confusion	6 (1.6)
Other	42 (10.9)

*Criteria not mutually exclusive; [†]Respondents have no definition of resistant alcohol withdrawal; and [‡]Respondents do not see resistant alcohol withdrawal often in their practice.

were Hack, 103 (26.8%); Benedict, 108 (28.1%); Hughes, 109 (28.4%); and 65 (16.9%) did not respond; 222 (57.8%) respondents said these definitions were not equivalent.

DISCUSSION

Clinicians' individual definitions of resistant alcohol withdrawal are largely based on the total benzodiazepine dose required to control symptoms. The median hourly dose provided by respondents is consistent with the literature-based definitions. However, no single definition of resistant alcohol withdrawal was preferred, because answers were distributed equally over notably distinct definitions.

This survey raises questions whether variability among clinicians in diagnosing resistant alcohol withdrawal affects patient outcome. The IQR calculated for high benzodiazepine dose partially illustrates that variation. Our results begin a discussion to improve understanding this entity. Resistant alcohol withdrawal should be suspected when using more than 40 mg of DEQ per hour and when the patient is worsening or not improving, despite closely repeated doses (seizures, persistent tachycardia, high score on assessment tool, and so on). This relatively new entity needs to be formally characterized in cohort studies to improve our understanding. Expert consensus could provide some definitional guidance to help future studies assess therapeutic interventions.

Strengths and limitations

Although we were unable to calculate cross-membership and ineligibility of individuals who received the link, we screened a large sample of clinicians using a rigorous method and provided a conservative participation rate. We pretested the questionnaire and allowed respondents to add information to their answers if desired. The dropout rate was 15.2%. The same link included a second survey addressing different clinical questions about alcohol withdrawal, which will be discussed separately, and might have prolonged the survey duration contributing to dropout. Deployment during summer months in the Northern hemisphere could have limited the response rate. Multiple reminders could have improved the response rate.

Additionally, we surveyed members of clinical toxicology and emergency medicine associations, which may

limit the generalization of our results. However, alcohol withdrawal is often diagnosed and treated in emergency departments with the assistance of clinical toxicologists.^{11,12} A selection bias may have been created by using a convenience sample of associations. Also, the term *persistent tachycardia* was not clearly defined, which may have led to wide interpretation. We were unable to find previous works that either discussed heart rate range for persistent tachycardia or other addressed clinician opinions on this topic.

CONCLUSION

Resistant alcohol withdrawal is an ill-defined clinical entity of unknown prevalence, defined by high-dose benzodiazepines (more than 40 mg of DEQ per hour), seizures, and tachycardia. We hope our findings guide future consensus work towards a formalized definition that allows future standardized research to ultimately improve patient care in terms of a reduction in mortality, morbidity, and health system costs.

SUPPLEMENTARY MATERIAL

The supplementary material for this article can be found at <https://doi.org/10.1017/cem.2019.421>.

Competing interests: None declared.

REFERENCES

1. Long D, Long B, Koyfman A. The emergency medicine management of severe alcohol withdrawal. *Am J Emerg Med* 2017;35(7):1005–11.
2. Rehm J, Mathers C, Popova S, et al. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet* (London, England) 2009;373(9682):2223–33.
3. Mayo-Smith MF. Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. *JAMA* 1997;278(2):144–51.
4. Lejoyeux M, Solomon J, Ades J. Benzodiazepine treatment for alcohol-dependent patients. *Alcohol Alcohol* 1998;33(6):563–75.
5. Hack JB, Hoffmann RS, Nelson LS. Resistant alcohol withdrawal: does an unexpectedly large sedative requirement identify these patients early? *J Med Toxicol* 2006;2(2):55–60.
6. Hughes D. Benzodiazepine-refractory alcohol withdrawal. REBEL EM; 2016 [updated April 28, 2016]. Available at:

- <http://rebelem.com/benzodiazepine-refractory-alcohol-withdrawal/> (accessed January 13, 2019).
7. Benedict NJ, Wong A, Cassidy E, et al. Predictors of resistant alcohol withdrawal (RAW): a retrospective case-control study. *Drug Alcohol Depend* 2018;192:303–8.
 8. Eysenbach G. Improving the quality of Web surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). *J Med Internet Res* 2004;6(3):e34.
 9. Dundee JW, McGowan WAW, Lilburn JK, McKay AC, Hegarty JE. Comparison of the actions of diazepam and lorazepam. *Br J Anaesth* 1979;51:439–46.
 10. US National Library of Medicine. ClinicalTrials.gov. Clinical quality improvement of benzodiazepine-resistant alcohol withdrawal syndrome (NCT01652326); 2012. Available at: <https://clinicaltrials.gov/ct2/show/NCT01652326> (accessed October 4, 2017).
 11. Hoskins R, Bengner J. What is the burden of alcohol-related injuries in an inner city emergency department? *Emerg Med J* 2013;30(3):e21.
 12. Cherpitel CJ, Ye Y. Trends in alcohol- and drug-related emergency department and primary care visits: data from four U.S. national surveys (1995–2010). *J Stud Alcohol Drugs* 2012;73(3):454–8.