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Review of acamprosate pharmacokinetics and dosing strategies

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Abstract

Introduction: Alcohol use disorder (AUD) is associated with significant morbidity and mortality, contributing to 5% of annual deaths. Although some literature suggests that acamprosate is an effective treatment for AUD, its traditional dosing regimen of 2 tablets 3 times daily may challenge patient adherence. This review compares clinical and pharmacokinetic data of different acamprosate dosing regimens to provide guidance on optimal dosing for treating AUD.

Methods: A comprehensive literature search was performed for articles published before March 2024. Relevant randomized controlled trials, case reports, and pharmacokinetic studies were identified from PubMed, PubMed Central, and Google Scholar.

Results: Three dosing regimens were identified, including traditional dose, reduced dose, and reduced frequency. Definitive conclusions regarding the comparative efficacy of these regimens cannot be drawn. However, reduced doses appear safe and efficacious in small clinical trials, and a pharmacokinetic study found reduced frequency to be bioequivalent to traditional doses.

Discussion: Adherence to pharmacotherapy for AUD is challenging and difficult to measure. A reduced dose regimen may be appropriate for patients who struggle with the pill burden of traditional doses, though the varying number of tablets required at different times may still pose adherence issues. The bioequivalence of reduced frequency dose to traditional dose suggests it could be a viable option for patients who find a 3-time daily frequency cumbersome. However, the lack of data on the clinical efficacy of reduced frequency makes it difficult to recommend as a primary regimen. Further research is needed to determine if either reduced dose or reduced frequency regimens could improve patient adherence compared with a traditional dose.

Keywords: acamprosate, alcohol use disorder, adherence, pharmacokinetics

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Introduction

Alcohol use disorder (AUD) is a leading cause of premature death in people aged 15 to 49 years. According to the World Health Organization, 2.6 million deaths globally were attributed to alcohol consumption in 2019.[1] Acamprosate is a first-line treatment option for AUD per the National Institute for Health and Care Excellence and American Psychiatric Association Guidelines.[2,3] It is theorized that acamprosate exerts its effects by counterbalancing the neurochemical disruptions induced by chronic

alcohol use on the excitatory neurotransmitter glutamate and the inhibitory neurotransmitter gamma-aminobutyric acid. In 2004, acamprosate gained FDA approval based on compelling evidence from 3 randomized, placebo-controlled European trials showcasing its efficacy over placebo in sustaining abstinence.[4-7] Despite initial promising findings, subsequent research, such as the COMBINE study in the United States, has yielded conflicting results. The COMBINE trial failed to demonstrate significant differences in abstinent days or median days to relapse between acamprosate and placebo, whether used alone or in combination with naltrexone or behavioral intervention.[8] This incongruity in efficacy outcomes may stem from reduced adherence in real-world settings compared with controlled research environments. While a 2022 systematic review reported acamprosate adherence rates of 85% to 90% in clinical trials, the reliability of this estimate is low because of inconsistent methods of monitoring and measuring adherence across studies.[9] More recently, the ADAM trial reported much lower patient-reported adherence in a real-world setting, with a mean adherence of only 37% at 6 months and 21.6% at 12 months among 255 participants taking acamprosate without adjunctive contingency or medication management strategies.[10] Adherence to acamprosate may be particularly challenging for several reasons. Although generally well-tolerated, up to 16% of patients may experience moderate diarrhea. While this side effect typically resolves after 4 weeks of consistent use, it could deter adherence early in treatment.[11] Additionally, negative cultural associations with the 666-mg recommended dose may influence patient acceptance.[12,13] However, the primary challenge may lie in the dosing regimen. The FDA-approved regimen requires two 333-mg tablets by mouth 3 times daily, totaling 1998 mg daily.[7] This high pill burden and frequent dosing may reduce adherence.[12,13] Simplified dosing regimens could improve outcomes, particularly if adherence issues contribute to efficacy differences between studies. For instance, a randomized controlled trial comparing oral naltrexone with placebo found no significant differences in drinking outcomes across 175 patients with AUD.[14] However, in a subgroup analysis of 70 patients with at least 80% adherence, the naltrexone cohort reported significant reductions in alcohol consumption and cravings. These results led to the development of once-monthly injectable naltrexone (Vivitrol) to enhance adherence.[15,16] Unfortunately, no long-acting formulations currently exist for acamprosate. This review aims to evaluate pharmacokinetic and clinical data supporting alternative oral acamprosate dosing regimens with implications related to enhancing patient adherence rates.

Methods

A literature search was performed using PubMed, PubMed Central, and Google Scholar databases to identify relevant articles published before March 2024. The search strategy involved the combination of keywords "acamprosate" AND "efficacy" AND "alcohol" as well as "acamprosate" AND "pharmacokinetics" AND "alcohol." The inclusion criteria encompassed English-language clinical trials, practice guidelines, reviews, and case reports conducted in human subjects without restriction on publication date. Included were articles that examined outcomes related to acamprosate pharmacokinetics or its safety or efficacy in the treatment of AUD. Articles written in a language other than English, with animal subjects, or exclusively discussing acamprosate dosing of 666 mg by mouth 3 times daily were excluded from consideration.

Results

Search results yielded 5 studies, including 4 randomized controlled trials and 1 review. In addition to traditional dosing, 2 alternative dosing regimens were identified. The different dosing regimens are defined below; these titles will be used throughout.

1. Traditional dose: Acamprosate 1998 mg daily (two 333 mg tablets by mouth 3 times daily)
2. Reduced dose: Acamprosate 1332 mg per day (two 333 mg tablets by mouth in the morning, one 333 mg tablet by mouth midday, and one 333 mg tablet by mouth in the evening)
3. Reduced frequency:
   - Acamprosate 1998 mg per day (three 333 mg tablets by mouth twice daily)
   - Acamprosate 2000 mg per day (two 500 mg tablets by mouth twice daily, though this tablet strength is not commercially available)

Results from the randomized clinical trials are displayed in Table 1. Three clinical trials examined reduced dose acamprosate, while 1 examined reduced frequency acamprosate.

Additionally, a review of acamprosate's clinical pharmacokinetics by Saivin et al[18] was identified via the same search strategy. This review summarizes another article by the same authors, titled "Bioequivalence study for highly variable drugs: the example of acamprosate," which is listed as "in press" in *Pharmaceutical Research*.[19] However, a search of that journal's archives did not yield this article, and further searches of PubMed, PMC, and Google Scholar were also unsuccessful. Despite its unavailability, the article is relevant to this paper as it examines the pharmacokinetics of reduced frequency acamprosate.

According to the review by Saiven et al,[18] the study aimed to establish the bioequivalence of traditionally dosed acamprosate with reduced frequency acamprosate using twice-daily dosing of two 500-mg tablets, a tablet strength that was developed to improve patient adherence.[18] The study used a crossover design with 2 groups as follows: half of the participants received traditional dosed acamprosate for 9 days, followed by reduced frequency for the next 9 days, while the other half followed the inverse order. Twelve healthy volunteers were included in each group, totaling a

TABLE 1: Randomized controlled trial results

Author	Study Characteristics	Intervention	Selected Results
Pelc[4] (1997)	**Study design (duration):** RCT (14-day intervention period, 90-day follow-up) **Setting:** 11 centers in Belgium and France **Patient population (sample size):** Age > 18 years, AUD defined by DSM-III, N = 188 (traditional dose group, 63; reduced dose group, 63 placebo, 62)	Traditional dose acamprosate vs reduced dose acamprosate vs placebo	Outcome: traditional dose vs reduced dose vs placebo, *P*: • Median cumulative time abstinent at day 90 (d): 56.6 vs 51.9 vs 34.3, <0.05 • Proportion abstinent at day 90 (%): 51 vs 44 vs 26, <0.05 • Proportion continuously abstinent through 90 days (%): 41 vs 41 vs 15, <0.001 • Median time to first relapse (d): 56.3 vs 55.5 vs 15, <0.001 • CGI scale: Statistically significantly higher than placebo in both treatment arms by day 15 through 90, $P < 0.05$ • No subjective desire for alcohol by day 90 (%): 58% vs 57% vs 31%, <0.03 • Overwhelming desire for alcohol by day 90: 22% placebo vs 13% reduced dose vs 11% traditional dose • Diarrhea: 48% traditional dose vs 43% reduced dose vs 39% placebo, ns (traditional dose vs reduced dose)
Paille[5] (1995)	**Study design (duration):** RCT (7- to 28-day intervention period, 12-month follow-up) **Setting:** 31 centers in France **Patient population (sample size):** Age > 18 years, AUD defined by DSM-III, N = 538 (traditional-dose group, 173; reduced-dose group, 188; placebo, 177)	Traditional dose acamprosate vs reduced dose acamprosate vs placebo	Outcome: traditional dose vs reduced dose vs placebo, *p*: • Proportion continuously abstinent through 12 months (%): 19.1 vs 18.1 vs 11.3, <0.096 • Proportion abstinent at 12 month assessment (%) 34.7 vs 27.7 vs 18.6, <0.001 • Mean cumulative time abstinent (d): 223 vs 198 vs 173, 0.0005 (traditional dose vs placebo), $P = 0.055$ (reduced dose vs placebo) • Mean time to first relapse (d): 153 vs 135 vs 102, 0.032 • Clinic attendance: 54.9% vs 47.3% vs 35.6%, 0.005 • Diarrhea: 21 vs 14 vs 6, <0.01 (traditional dose vs reduced dose)
Niederhofer[6] (2003)	**Study design (duration):** RCT (5-day intervention period, 12-month follow-up) **Setting:** 1 center in Austria **Patient population (sample size):** Age 16-19 years, AUD defined by DSM-IV, N = 26 (reduced-dose group, 13; placebo, 13)	Reduced dose acamprosate vs placebo	Outcome: reduced dose vs placebo, *P*: • Proportion abstinent at day 90 assessment (%): 33.3% vs 9.5%, 0.0076 • Mean cumulative time abstinent by day 90 (d): 79.8 vs 32.8, 0.012 • Side effects (ns)
Hammarberg[17] (2004)	**Study design (duration):** RCT (5-day intervention period, 12-month follow-up) **Setting**: 1 center in Sweden **Patient population (sample size):** Age > 18 years, AUD defined by DSM-IV, N = 70 (MPI, 36; EPI, 34)	MPI with reduced frequency acamprosate (using 333-mg tablets) vs EPI with reduced frequency acamprosate	Outcome: F statistic of baseline vs week 24 in all completers, *P*: • Decline in heavy drinking days: 49.4, <0.001 • Decline in number of drinking days: 36.1, <0.001 • Adherence to acamprosate via urine test at week 24 in all patients: 80.9%

AUD = alcohol use disorder; CGI = clinical global impression; DSM-III = *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition; EPI = extended psychosocial intervention; MPI = minimal psychosocial intervention; ns = nonsignificant; RCT = randomized control trial.

sample size of 24. Blood samples were collected over 24-hour periods on days 8 and 9, as well as on days 17 and 18, to mimic typical time to acamprosate steady state. Terminal decay was followed up on day 23. Drug plasma concentrations were compared between both dosing strategies at multiple time points throughout the 24-hour collection period. They followed a similar curve, with no statistically significant differences found at any point.[18]

Discussion

Five trials investigating different acamprosate dosing regimens were identified. Most randomized controlled trials were characterized by smaller sample sizes and often high dropout rates due to relapse. The endpoints assessed across these trials included duration of abstinence, relapse rates, and incidence of diarrhea.[4-6,17,18] Two trials examined acamprosate adherence rates using either pill counts or urine testing.[4,17] Based on the efficacy, safety, and pharmacokinetic data reviewed, several promising acamprosate dosing regimens emerge, each with its own advantages and challenges. A summary of these points can be found in Table 2.

Traditional Dose

The FDA-approved traditional acamprosate dosing regimen is the most extensively studied in terms of efficacy and safety. It is the regimen with which many clinicians are most familiar. However, adherence to this regimen has been shown to be inconsistent in real-world environments.[4,10] This is likely due to the aforementioned difficulties related to high pill burden, frequent dosing, and negative cultural associations with the 666-mg dose.[9,12] When considering traditional dosing, it should be noted that patient-specific factors like lifestyle, daily routine, and cognitive function may influence a patient's ability to adhere consistently to a 3-times daily regimen. The added pill burden from concurrent medications, particularly in individuals managing multiple chronic conditions, could exacerbate pill fatigue and further hinder adherence. Moreover, cultural considerations surrounding the significance of the 666-mg dose should not be overlooked. Within Christianity, it is referred to as the "number of the beast" and is associated with the devil.[13] These negative connotations may impact patient acceptance of treatment.[12] Clinicians should engage in culturally sensitive discussions to address any beliefs patients may have regarding the treatment regimen. Such considerations should guide clinical decision-making to optimize treatment outcomes for patients with AUD.

Reduced Dose

Owing to the poor bioavailability of acamprosate, estimated at approximately 10%, it has been assumed that larger doses are necessary to achieve clinical effects.[19] However, a pharmacokinetic study demonstrated that acamprosate absorption rates are

TABLE 2: Advantages and disadvantages of 3 reviewed acamprosate dosing regimens

	Advantages	Disadvantages
Traditional dose Acamprosate 1998 mg daily (two 333 mg tablets by mouth 3 times daily)	Robust clinical and safety data Clinician familiarity with dosing	Frequent 3 times daily dosing High pill burden (6 tablets)
Reduced dose Acamprosate 1332 mg daily (two 333 mg tablets by mouth in the morning, one 333 mg tablet midday, and one 333 mg tablet in the evening)	Reduced pill burden compared to traditional dosing (4 tablets) May have decreased dose-related side effects compared to traditional dosing (ie, diarrhea)	Complex regimen with inconsistent number of tablets at different 3 of day Frequent 3 times daily dosing
Reduced frequency Acamprosate 1998 mg daily (three 333 mg tablets by mouth twice daily) Acamprosate 2000 mg per day (two 500 mg tablets by mouth twice daily)	Twice daily dosing may facilitate improved adherence in patients struggling with 3 times daily regimens Pharmacokinetic data suggests similar serum concentrations to traditional dosing	High pill burden (6 tablets) Minimal clinical data and no comparison to other dosing regimens or placebo No safety data regarding whether increasing dose strength results in an increase dose-related side effects (ie, diarrhea) 500-mg tablet strength is not commercially available

not increased with increasing doses, questioning the need for dose titration.[18] In addition, higher doses may increase the risk of side effects like diarrhea.[12]

The study by Paille et al[5] found no significant difference in the proportion of patients who maintained abstinence at 12 months when comparing reduced dose acamprosate with traditional dosing.[5] Pelc et al[4] confirmed these findings, demonstrating that reduced dose acamprosate had comparable outcomes to traditional dosing in terms of time to relapse, cumulative time abstinent, and continuous time abstinent at 90 days. Additionally, all clinical outcomes with reduced dosing proved to be more efficacious than placebo. These results suggest that lower doses may have similar efficacy to that of the traditional dosing regimen.

Regarding side effects, Pelc et al[4] and Niederhofer et al[6] reported similar rates of diarrhea when comparing reduced dose acamprosate with traditional dosing, while Paille et al[5] observed significantly lower rates of diarrhea in the reduced dose cohort. Although diarrhea is often considered a dose-dependent side effect, the discrepancy between studies may be partly due to a high baseline rate of diarrhea commonly seen in patients with AUD. Of note, no study showed a statistically significant increase in diarrhea when using the reduced-dose acamprosate. Providers could consider using this regimen in patients who experience bothersome diarrhea as a side effect of traditional-dose acamprosate.

Adherence rates varied among studies assessing reduced dose acamprosate. One trial reported excellent adherence rates exceeding 95%, confirmed via pill count, while another reported a dropout rate greater than 50%, complicating the assessment of adherence and patient satisfaction.[4,17] Although these studies do not show higher adherence rates with reduced dose acamprosate, clinicians might consider this dosing scheme in patients who prefer a lower pill burden. However, the regimen maintains a 3 times daily frequency that could be inconvenient for some patients. Additionally, the regimen involves an inconsistent tablet amount at different times of the day as follows: 2 tablets in the morning and 1 tablet at midday and night. This may pose a challenge for patients to remember, particularly those with cognitive issues. If clinicians decide to use reduced-dose acamprosate, it is advisable to assess these factors and provide adherence support, such as reminder calendars or pill boxes.

Reduced Frequency

Of particular interest to this review is the reduced-frequency dosing regimen, as it may be preferred by patients for its relative ease of use. In a review of pharmacokinetic data, reduced-frequency acamprosate showed similar serum concentrations when compared with traditional dosing.[18,19] The regimen was assessed in a small group of healthy young adults, which may not be the most reflective of the patient population of interest. However, as acamprosate is not hepatically metabolized and pharmacodynamic studies have shown that there is no effect on acamprosate with alcohol consumption, these bioequivalence data are likely applicable to patients with AUD and liver dysfunction.[10,21,22] Of note, this study used a regimen of two 500-mg tablets of acamprosate taken twice daily, a tablet strength that is not commercially available. This dose was approximated by Hammarberg et al,[17] who used 3 commercially available 333-mg tablets taken twice daily, providing nearly the same total amount of the drug per dose.

There is limited clinical data evaluating reduced frequency acamprosate. Hammarberg et al[17] studied 2 patient populations prescribed the regimen when comparing different methods of psychological intervention. This study provides meaningful adherence data for the reduced frequency regimen, although it is challenging to determine whether clinical benefits were attributable to acamprosate or psychological interventions. Urine tests indicated that acamprosate adherence was greater than 80% in both groups at week 24. However, the study did not provide data regarding adverse events, raising questions about whether there may be an increased risk of diarrhea associated with higher strength of acamprosate per dose.[17] Despite promising pharmacokinetic data, the safety and efficacy of reduced frequency acamprosate compared with traditional dosing cannot be adequately assessed without comparative studies. Further research is needed to address these questions. In the interim, clinicians may consider reduced frequency acamprosate for patients struggling with a 3 times daily dosing schedule, with the understanding that its efficacy and safety are not yet fully established.

Limitations

Limitations of this review include the absence of articles directly comparing all 3 acamprosate dosing regimens. Traditional dosing has been the most extensively studied, with a moderate amount of evidence comparing it with reduced-dose regimens. No articles were identified that compared clinical outcomes of reduced frequency acamprosate with other regimens, though pharmacokinetic data suggest bioequivalence to traditional dosing. As previously noted, the study on bioequivalence does not appear to have been published; rather, it was referenced in a review by the same authors.[18] Significant dropout rates were observed across all included trials, often due to relapse, although the reasons were not always clearly described. The outcomes assessed and methods used varied across studies, complicating direct comparisons between regimens. All studies included in the review were conducted in Europe. As previously established, studies conducted in the United States have produced conflicting results with historical European trials. Methodological differences and the role of cultural differences regarding AUD treatment and social support systems may play a role in the discrepancy. Studies used

the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (published in 1980) and the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (published in 1994) for diagnosing AUD. Unlike the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, which requires 2 of 11 criteria for diagnosis of a substance use disorder, the 2 previous versions consisted of 2 categories for diagnosis, Substance Abuse and Substance Dependence.[23-25] The minimal changes in the assessment of substance use disorders likely had a negligible impact on population selection.

Conclusion

Management of AUD is complex, with pharmacotherapy being just one component of a comprehensive approach. Real-world data indicate that adherence to medications for AUD varies widely and is challenging to measure accurately. The lack of data directly comparing different dosing regimens represents an opportunity for future studies to confirm optimal dosing schemes. Pharmacokinetic studies suggest that twice daily acamprosate dosing may be an appropriate regimen to facilitate adherence. Improved patient adherence through decreased pill burden and dose-dependent side effects has been observed with reduced dose acamprosate while maintaining similar efficacy to traditional dosing. In the absence of such factors, the benefits of reduced dosing over traditional dosing are questionable. Therefore, considering patient-specific factors when choosing a dosing strategy may enhance efficacy and patient satisfaction.

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References

1. who.int [Internet]. Geneva: World Health Organization; c2024 [updated 2024 Jun 28; cited 2024 Jun 15]. Available from: https://www.who.int/news-room/fact-sheets/detail/alcohol
2. National Collaborating Centre for Mental Health. Alcohol-Use Disorders: Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence. British Psychological Society; 2011.
3. Reus VI, Fochtmann LJ, Bukstein O, et al. The American Psychiatric Association Practice Guideline for the Pharmacological Treatment of Patients With Alcohol Use Disorder. Am J Psychiatry. 2018;175(1):86-90. DOI: 10.1176/appi.ajp.2017.1750101
4. Pelc I, Verbanck P, Le Bon O, Gavrilovic M, Lion K, Lehert P. Efficacy and safety of acamprosate in the treatment of detoxified alcohol-dependent patients. A 90-day placebo-controlled dose-finding study. Br J Psychiatry. 1997;171:73-7. DOI: 10.1192/bjp.171.1.73
5. Paille FM, Guelfi JD, Perkins AC, Royer RJ, Steru L, Parot P. Double-blind randomized multicentre trial of acamprosate in maintaining abstinence from alcohol. Alcohol Alcohol. 1995;30(2):239-47. PMID: 7662044
6. Niederhofer H, Staffen W. Acamprosate and its efficacy in treating alcohol dependent adolescents. Eur Child Adolesc Psychiatry. 2003;12(3):144-8. DOI: 10.1007/s00787-003-0327-1
7. Acamprosate [package insert]. St. Louis, MO. Forest Pharmaceuticals, Inc.; 2004.
8. Anton RF, O'Malley SS, Ciraulo DA, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA. 2006;295(17):2003-17. DOI: 10.1001/jama.295.17.2003
9. Donoghue K, Hermann L, Brobbin E, Drummond C. The rates and measurement of adherence to acamprosate in randomised controlled clinical trials: a systematic review. *PLoS One*. 2022;17(2):e0263350. DOI: 10.1371/journal.pone.0263350
10. Donoghue K, Boniface S, Brobbin E, et al. Adjunctive medication management and contingency management to enhance adherence to acamprosate for alcohol dependence: the ADAM trial RCT. Health Technol Assess. 2023;27(22):1-88. DOI: 10.3310/DQKL6124
11. Witkiewitz K, Saville K, Hamreus K. Acamprosate for treatment of alcohol dependence: mechanisms, efficacy, and clinical utility. Ther Clin Risk Manag. 2012;8:45-53. DOI: 10.2147/TCRM.S23184
12. D'Souza R. The importance of spirituality in medicine and its application to clinical practice. Med J Aust. 2007;186(S10):S57-9. DOI: 10.5694/j.1326-5377.2007.tb01043.x
13. Beale GK. The Book of Revelation: A Commentary on the Greek Text. Eerdmans; 2008.
14. Chick J, Anton R, Checinski K, et al. A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse. Alcohol Alcohol. 2000;35(6):587-93. DOI: 10.1093/alcalc/35.6.587
15. Srivastava AB, Gold MS. Naltrexone: a history and future directions. Cerebrum. 2018;2018:cer-13-18. PMCID: PMC6353110
16. Naltrexone [package insert]. Pomona, NY. Duramed Pharmaceuticals, Inc.; 2013.
17. Hammarberg A, Wennberg P, Beck O, Franck J. A comparison of two intensities of psychosocial intervention for alcohol dependent patients treated with acamprosate. Alcohol Alcohol. 2004;39(3):251-5. DOI: 10.1093/alcalc/agh056
18. Saivin S, Hulot T, Chabac S, Potgieter A, Durbin P, Houin G. Clinical pharmacokinetics of acamprosate. Clin Pharmacokinet. 1998;35(5):331-45. DOI: 10.2165/00003088-199835050-00001
19. Saivin S, Hulot T, Theodor R, et al. Bioequivalence study for highly variable drugs: the example of acamprosate. Pharm Res. Forthcoming.
20. Kufahl PR, Watterson LR, Olive MF. The development of acamprosate as a treatment against alcohol relapse. Expert Opin Drug Discov. 2014;9(11):1355-69. DOI: 10.1517/17460441.2014.960840
21. Bujarski S, Ray LA. Experimental psychopathology paradigms for alcohol use disorders: Applications for translational research. Behav Res Ther. 2016;86:11-22. DOI: 10.1016/j.brat.2016.05.008
22. Caputo F, Domenicali M, Bernardi M. Diagnosis and treatment of alcohol use disorder in patients with end-stage alcoholic liver disease. Hepatology. 2019;70(1):410-7. DOI: 10.1002/hep.30358
23. Robinson SM, Adinoff B. The classification of substance use disorders: historical, contextual, and conceptual considerations. Behav Sci (Basel). 2016;6(3):18. DOI: 10.3390/bs6030018
24. American Psychiatric Association. Diagnostic and statistical manual III. APA Press; 1980.
25. American Psychiatric Association. Diagnostic and statistical manual IV. APA Press; 1994.