

Safer use of benzodiazepines for alcohol detoxification



© IMAGES.COM/CORBIS

David R. Spiegel, MD
Associate Professor of Clinical Psychiatry

Neeta Kumari, MD
Psychiatry Resident

Justin D. Petri, MD
Assistant Professor of Psychiatry

••••

Eastern Virginia Medical School
Norfolk, VA

To avoid excessive dosing, be alert for falsely elevated CIWA-Ar scores

Clinicians often use the symptom-triggered Clinical Institute Withdrawal Assessment for Alcohol Scale, Revised (CIWA-Ar)¹ to assess patients' risk for alcohol withdrawal because it has well-documented reliability, reproducibility, and validity based on comparison with ratings by expert clinicians.^{2,3} The CIWA-Ar commonly is used to determine when to administer lorazepam to limit or prevent morbidity and mortality in patients who are at risk of or are experiencing alcohol withdrawal. Refined to a list of 10 signs and symptoms, the CIWA-Ar is easy to administer and useful in a variety of clinical settings. The maximum score is 67, and patients with a score >15 are at increased risk for severe alcohol withdrawal.¹ For a downloadable copy of the CIWA-Ar, see this article at CurrentPsychiatry.com.

Despite the benefits of using the CIWA-Ar, qualitative description of certain alcohol withdrawal symptoms is prone to subjective misinterpretation and can result in falsely elevated scores, excessive benzodiazepine administration, and associated sequelae.⁴ This article describes such a scenario, and examines factors that can contribute to a falsely elevated CIWA-Ar score.

CASE REPORT

Resistant alcohol withdrawal

Mr. J, age 24, is referred to the consultation-liaison service at our teaching hospital for "overall psychiatric assessment and help with alcohol withdrawal." When brought to the hospital, Mr. J was experiencing diaphoresis and tachycardia. During the interview, he says he "experiences withdrawal symptoms all the time, so I am familiar with the signs."

Causes and treatment of alcohol withdrawal symptoms

Common symptoms of alcohol withdrawal include autonomic hyperactivity, tremor, insomnia, nausea, vomiting, agitation, anxiety, grand mal seizures, and transient visual, tactile, or auditory hallucinations.⁵ These symptoms result, in part, from the effects of chronic alcohol exposure on brain γ -aminobutyric acid (GABA) and glutamate systems. Alcohol acutely enhances presynaptic GABA release through allosteric modulation at GABA_A receptors and inhibits glutamate function through antagonism of *N*-methyl-D-aspartate (NMDA) receptors. Chronic alcohol exposure elicits compensatory downregulated GABA_A and upregulated NMDA expression.

When alcohol intake abruptly stops and its acute effects dissipate, the sudden reduction in GABAergic tone and increase in glutamatergic tone cause alcohol withdrawal symptoms.⁶ Benzodiazepines, which bind at the benzodiazepine site on the GABA_A receptor and, similar to alcohol, acutely enhance GABA and inhibit glutamate signaling, are the standard of care for alcohol withdrawal because they reduce anxiety and the risk of seizures and delirium tremens, which is a severe form of alcohol withdrawal characterized by disturbance in consciousness and cognition and hallucinations.^{5,6}

Mr. J is cooperative with the interview. Psychomotor agitation or retardation is not noted. His speech is goal-directed, his mood is "calm," and his affect is within normal range. His thought content is devoid of psychoses or lethal ideations. On Mini-Mental State Examination, Mr. J scores 28 out of 30, which indicates normal cognitive functioning. He reports drinking eight 40-oz bottles of beer daily for the past 3 months. He started drinking alcohol at age 14 and has had only one 1-year period of sobriety. He denies using illicit drugs and his urine drug screen is unremarkable. Mr. J has a history of delirium tremens (DTs), no significant medical history, and was not taking any medications when admitted. His psychiatric history includes generalized anxiety disorder (GAD) and antisocial personality disorder and his family history is significant for alcohol dependence.

Laboratory workup is unremarkable except for a blood alcohol level of 0.23%. Review of systems is significant for mild tremor but no other symptoms of alcohol withdrawal. Physical examination is within normal limits.

Mr. J is started on a symptom-trigger alcohol detoxification protocol using the CIWA-Ar. Based on an elevated CIWA-Ar score of 33, he receives lorazepam IV, 11 mg on his first day of hospitalization and 8 mg on the second day. On the third day, Mr. J is agitated and pulls his IV lines in an attempt to leave. Over the next 24 hours, his blood pressure ranges from 136/90 mm Hg to 169/92 mm Hg and his pulse ranges from 94 to 115 beats per

minute. He is given lorazepam, 30 mg, and is transferred to the intensive care unit (ICU).

At this time, Mr. J's Delirium Rating Scale (DRS) score is 20 (maximum: 32). He remains in the ICU on lorazepam, 25 mg/hr. After 3 days in the ICU, lorazepam is titrated and stopped 2 days later. After lorazepam is stopped, Mr. J's DRS score is 0, his vital signs are stable, and he no longer demonstrates signs or symptoms of DTs or alcohol withdrawal. He is discharged 1 day later.

Symptom-triggered treatment

Alcohol withdrawal symptoms mainly are caused by the effects of chronic alcohol exposure on brain γ -aminobutyric acid (GABA) and glutamate systems; benzodiazepines are the standard of care (*Box*).^{5,6} Mr. J had a history of DTs, which is a risk factor for more severe alcohol withdrawal symptoms and recurrence of DTs.⁷ Some authors report that fixed dosing intervals are the "gold standard therapy" for alcohol withdrawal, and may be preferable for patients with a history of DTs.⁸ However, Mr. J was placed on a symptom-triggered protocol, which is standard at our hospital. The decision to implement this protocol was based on concerns of oversedation and possible respiratory suppression. Clinical trials have demonstrated that compared with fixed scheduled therapy for alcohol withdrawal, symptom-triggered protocols result in a reduced need for benzodiazepines (*Table, page 12*).

Clinical Point

Clinical trials demonstrated that symptom-triggered protocols for alcohol withdrawal result in a reduced need for benzodiazepines

See this article at

CurrentPsychiatry.com
for a downloadable copy
of the CIWA-Ar



Alcohol withdrawal

Clinical Point

Pulse and blood pressure elevations occur in alcohol withdrawal, but other signs are more reliable in assessing severity



Discuss this article at www.facebook.com/CurrentPsychiatry

Table

Benefits of symptom-triggered vs fixed scheduled therapy for alcohol withdrawal

	ST	FS	Benefits of ST
Efficacy in alcohol withdrawal	Yes	Yes	
Flexibility in dosing with fluctuations in CIWA-Ar score	Yes	No	Less medication can be given overall if alcohol withdrawal signs resolve rapidly
Lower total benzodiazepine doses	+	-	Smaller chance of side effects such as oversedation, paradoxical agitation, delirium due to benzodiazepine intoxication, or respiratory depression
Fewer complications of higher benzodiazepine doses	+	-	Reduced risk of prolonged hospitalization, morbidity from aspiration pneumonia, or need to administer a reversal agent such as flumazenil

+ = more likely; - = less likely
 CIWA-Ar: Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised; FS: fixed scheduled; ST: symptom-triggered
 For a bibliography, see this article at CurrentPsychiatry.com

This treatment strategy requires frequent patient reevaluations—particularly early on—with attention to signs and symptoms of alcohol withdrawal and excessive sedation from medications. Additionally, although most patients with alcohol withdrawal respond to standard treatment that includes benzodiazepines, optimal nutrition, and good supportive care, a subgroup may resist therapy (resistant alcohol withdrawal). Therefore, Mr. J—and others with resistant alcohol withdrawal—may require large doses of benzodiazepines and additional sedatives and undergo complicated hospitalizations.⁹ Nonetheless, as exemplified by Mr. J, symptom-triggered protocols for alcohol withdrawal can result in potential morbidity and mortality.

Factors influencing CIWA-Ar score

Vital signs monitoring. One limitation of the CIWA-Ar is that vital signs—an objective measurement of alcohol withdrawal—are not used to determine the score. Indeed, Mr. J presented with vital sign dysregulation. However, research suggests that the best predictor of high withdrawal scores includes groups of symptoms rather than individual symptoms.¹⁰ In that study, pulse and blood pressure did not correlate with withdrawal severity. Pulse and blood pressure elevations occur in alcohol withdrawal, but other signs and symptoms are more reliable in assessing withdrawal severity.

This is clinically important because physicians often prescribe medications for alcohol withdrawal treatment based on pulse and blood pressure measures.¹ This needs to be balanced against research that found a systolic blood pressure >150 mm Hg and axillary temperature >38°C can predict development of DTs in patients experiencing alcohol withdrawal.⁷

Lorazepam-induced disinhibition. Benzodiazepines affect functions associated with processing within the orbital prefrontal cortex,¹¹ including response inhibition and socially acceptable behavior, and impairment in this functioning can result in behavioral disinhibition.¹² This effect could account for the apparent paradoxical clinical observation of aggression in benzodiazepine-sedated patients.¹³ Because agitation is scored on the CIWA-Ar,^{1,10} falsely elevated scores caused by interpreting benzodiazepine-induced aggression as agitation could result in patients (such as Mr. J) receiving more lorazepam, therefore perpetuating this cycle.

Comorbid anxiety disorders also could falsely accentuate CIWA-Ar scores. For example, the odds of an alcohol dependence diagnosis are 2 to 3 times greater among patients with an anxiety disorder.¹⁴ Additionally, the lifetime prevalence of comorbid alcohol dependence for patients with GAD—such as Mr. J—is 30% to 35%.^{14,15}

Alcohol withdrawal can be more severe in patients with alcohol dependence and anxiety disorders because evidence suggests the neurochemical processes underlying both are similar and potentially additive. Studies have shown that these dual diagnosis patients experience more severe symptoms of alcohol withdrawal as assessed by total CIWA-Ar score than those without an anxiety disorder.¹⁵ Although such patients may require more aggressive pharmacologic treatment, the dangers of higher benzodiazepine dosages may be even greater.

Benzodiazepine-induced delirium. A recent meta-analysis suggested that benzodiazepines may be associated with an increased risk of delirium.¹⁶ Longer-acting benzodiazepines may be associated with increased risk of delirium compared with short-acting agents, and higher doses during a 24-hour period may be associated with increased risk of delirium compared with lower doses. However, wide confidence intervals imply significant uncertainty with these results, and not all patients in the studies reviewed were undergoing alcohol detoxification.¹⁶ Benzodiazepines have been reported to accentuate delirium when used to treat DTs.¹⁷

We postulate that although Mr. J received lorazepam—a short- to moderate-acting benzodiazepine with a half-life of 12 to 16 hours¹⁸—the cumulative dose was high enough to have accentuated—rather than attenuated—delirium.¹⁶

Personality disorders. Comorbid alcohol use disorders (AUDs) and personality disorders are well documented. One study found the prevalence of personality disorders in AUDs ranged from 22% to 78%.¹⁹ Psychologically, drinking to cope with negative subjective states and emotions (coping motives) and drinking to enhance positive emotions (enhancement motives) may explain the relation between Cluster B personality disorders and AUDs.²⁰

Research on prefrontal functioning in alcoholics and individuals with antisocial personality disorder symptoms has suggested that both groups may be impaired

on tasks sensitive to compromised orbitofrontal functioning.²¹ The orbitofrontal system is essential for maintaining normal inhibitory influences on behavior.²² Benzodiazepines can increase the likelihood of developing disinhibition or impulsivity, which are symptoms of antisocial personality disorder. Because Mr. J had antisocial personality disorder, treating his alcohol withdrawal with a benzodiazepine could have accentuated these symptoms, which were subsequently “treated” with additional lorazepam, therefore worsening the cycle.

Medical comorbidities. The CIWA-Ar relies on autonomic signs and subjective symptoms and was not designed for use in nonverbal patients in the ICU. It is possible that the presence of other acute illnesses may contribute to increased CIWA-Ar scores, but we are unaware of any studies that have evaluated such factors.²³

However, tremor, which is scored on the CIWA-Ar, can falsely elevate scores if it is caused by something other than acute alcohol withdrawal. Although essential tremors attenuate with acute alcohol use, chronic alcohol use can result in parkinsonism with a resting tremor, and cerebellar degeneration, which can include an action tremor and cerebellar 3-Hz leg tremor.²⁴ Finally, hepatic encephalopathy—a neuropsychiatric syndrome characterized by disturbances in consciousness, mood, behavior, and cognition—can occur in patients with advanced liver disease, which may be precipitated by alcohol use. The clinical presentation and symptom severity of hepatic encephalopathy varies from minor cognitive impairment to gross disorientation, confusion, and agitation,²⁵ all of which can elevate CIWA-Ar scores.

The role of disinhibition

Disinhibition could serve as the “final common pathway” through which CIWA-Ar scores can be falsely elevated.¹¹ For a *Figure* that illustrates this, see this article at CurrentPsychiatry.com. Mr. J presented with several variables that could have elevated his CIWA-Ar score; additional po-

Clinical Point

Benzodiazepines have been reported to accentuate delirium when used to treat delirium tremens

See this article at

CurrentPsychiatry.com

for a figure that details the role of disinhibition during alcohol detoxification



Alcohol withdrawal

Clinical Point

Tremor is scored on the CIWA-Ar and can falsely elevate scores if it is caused by something other than acute alcohol withdrawal

Related Resources

- Myrick H, Anton RF. Treatment of alcohol withdrawal. *Alcohol Health & Research World*. 1998;22(1):38-43. <http://pubs.niaaa.nih.gov/publications/arh22-1/38-43.pdf>.
- Amato L, Minozzi S, Davoli M. Efficacy and safety of pharmacological interventions for the treatment of the Alcohol Withdrawal Syndrome. *Cochrane Database Syst Rev*. 2011;(6):CD008537.

Drug Brand Names

Chlorpromazine • Thorazine	Olanzapine • Zyprexa
Clozapine • Clozaril	Quetiapine • Seroquel
Flumazenil • Romazicon	Risperidone • Risperdal
Haloperidol • Haldol	Ziprasidone • Geodon
Lorazepam • Ativan	

Disclosures

Dr. Spiegel is on the speaker's bureau of Sunovion Pharmaceuticals.

Drs. Kumari and Petri report no financial relationships with any company whose products are mentioned in this article or with manufacturers of competing products.

Acknowledgement

The authors thank Amy Herndon for her help in preparing this article.

tential factors include other psychiatric diagnoses such as bipolar disorder, opiate withdrawal, dementia, drug-seeking behavior, or malingering.^{26,27}

Treating disinhibition in patients with alcohol withdrawal. Continuing to administer escalating doses of benzodiazepines is counterintuitive for benzodiazepine-induced disinhibition. In a study of alcohol withdrawal in rats, antipsychotics evaluated had some beneficial effects on alcohol withdrawal signs.²⁸ In this study, the comparative effectiveness of atypical antipsychotics was as follows: risperidone = quetiapine > ziprasidone > clozapine > olanzapine.

The American Society of Addiction Medicine's practice guideline advises

against using antipsychotics as the sole agent for DTIs because these agents are associated with a longer duration of delirium, higher complication rates, and higher mortality.²⁸ However, antipsychotics have a role as an adjunct to benzodiazepines when benzodiazepines don't sufficiently control agitation, thought disorder, or perceptual disturbances. Although haloperidol use is well established in this scenario, chlorpromazine is contraindicated because it is epileptogenic, and little information is available on atypical antipsychotics.²⁹ If Mr. J had not responded to tapering lorazepam, evidence would support using haloperidol.


References

1. Sullivan JT, Sykora K, Schneiderman J, et al. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *Br J Addict*. 1989;84(11):1353-1357.
2. Knott DH, Lerner WD, Davis-Knott T, et al. Decision for alcohol detoxification: a method to standardize patient evaluation. *Postgrad Med*. 1981;69(5):65-69, 72-75, 78.
3. Wiehl WO, Hayner G, Galloway G. Haight Ashbury Free Clinics' drug detoxification protocols—Part 4: alcohol. *J Psychoactive Drugs*. 1994;26(1):57-59.
4. Bostwick JM, Lapid MI. False positives on the clinical institute withdrawal assessment for alcohol-revised: is this scale appropriate for use in the medically ill? *Psychosomatics*. 2004;45(3):256-261.
5. Diagnostic and statistical manual of mental disorders, 4th ed, text rev. Washington, DC: American Psychiatric Association; 2000.
6. Schacht JP, Randall PK, Waid LR, et al. Neurocognitive performance, alcohol withdrawal, and effects of a combination of flumazenil and gabapentin in alcohol dependence. *Alcohol Clin Exp Res*. 2011;35(11):2030-2038.
7. Monte R, Rabañal R, Casariego E, et al. Risk factors for delirium tremens in patients with alcohol withdrawal syndrome in a hospital setting. *Eur J Intern Med*. 2009;20(7):690-694.
8. Saitz R, O'Malley SS. Pharmacotherapies for alcohol abuse. *Withdrawal and treatment*. *Med Clin North Am*. 1997;81(4):881-907.
9. 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.
10. Pittman B, Gueorguieva R, Krupitsky E, et al. Multidimensionality of the Alcohol Withdrawal Symptom Checklist: a factor analysis of the Alcohol Withdrawal Symptom Checklist and CIWA-Ar. *Alcohol Clin Exp Res*. 2007;31(4):612-618.

Bottom Line

For patients experiencing alcohol withdrawal, several factors can falsely elevate scores on the Clinical Institute Withdrawal Assessment for Alcohol Scale, Revised including disinhibition, benzodiazepine-induced delirium, personality disorders, anxiety, and other psychiatric and medical comorbidities. Vigilance for these factors can help clinicians avoid administering excessive benzodiazepines, which can cause oversedation, respiratory distress, and other sequelae.

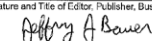
11. Deakin JB, Aitken MR, Dowson JH, et al. Diazepam produces disinhibitory cognitive effects in male volunteers. *Psychopharmacology* (Berl). 2004;173(1-2):88-97.
12. Hornberger M, Geng J, Hodges JR. Convergent grey and white matter evidence of orbitofrontal cortex changes related to disinhibition in behavioural variant frontotemporal dementia. *Brain*. 2011;134(pt 9):2502-2512.
13. Jones KA, Nielsen S, Bruno R, et al. Benzodiazepines - their role in aggression and why GPs should prescribe with caution. *Aust Fam Physician*. 2011;40(11):862-865.
14. Scott EL, Hulvershorn L. Anxiety disorders with comorbid substance abuse. *Psychiatric Times*. 2011;28(9).
15. Faingold CL, Knapp DJ, Chester JA, et al. Integrative neurobiology of the alcohol withdrawal syndrome—from anxiety to seizures. *Alcohol Clin Exp Res*. 2004;28(2):268-278.
16. Clegg A, Young JB. Which medications to avoid in people at risk of delirium: a systematic review. *Age Ageing*. 2011; 40(1):23-29.
17. Hecksel KA, Bostwick JM, Jaeger TM, et al. Inappropriate use of symptom-triggered therapy for alcohol withdrawal in the general hospital. *Mayo Clin Proc*. 2008;83(3):274-279.
18. Lader M. Benzodiazepines revisited—will we ever learn? *Addiction*. 2011;106(12):2086-2109.
19. Mellos E, Liappas I, Paparrigopoulos T. Comorbidity of personality disorders with alcohol abuse. *In Vivo*. 2010; 24(5):761-769.
20. Traggesser SL, Sher KJ, Trull TJ, et al. Personality disorder symptoms, drinking motives, and alcohol use and consequences: cross-sectional and prospective mediation. *Exp Clin Psychopharmacol*. 2007;15(3):282-292.
21. Oscar-Berman M, Valmas MM, Sawyer KS, et al. Frontal brain dysfunction in alcoholism with and without antisocial personality disorder. *Neuropsychiatr Dis Treat*. 2009;5:309-326.
22. Dom G, De Wilde B, Hulstijn W, et al. Behavioural aspects of impulsivity in alcoholics with and without a cluster-B personality disorder. *Alcohol Alcohol*. 2006;41(4):412-420.
23. de Wit M, Jones DG, Sessler CN, et al. Alcohol-use disorders in the critically ill patient. *Chest*. 2010;138(4):994-1003.
24. Mostile G, Jankovic J. Alcohol in essential tremor and other movement disorders. *Mov Disord*. 2010;25(14):2274-2284.
25. Crone CC, Gabriel GM, DiMartini A. An overview of psychiatric issues in liver disease for the consultation-liaison psychiatrist. *Psychosomatics*. 2006;47(3):188-205.
26. Reoux JP, Oreskovich MR. A comparison of two versions of the clinical institute withdrawal assessment for alcohol: the CIWA-Ar and CIWA-AD. *Am J Addict*. 2006;15(1):85-93.
27. Gray S, Borgundvaag B, Sirvastava A, et al. Feasibility and reliability of the SHOT: a short scale for measuring pretreatment severity of alcohol withdrawal in the emergency department. *Acad Emerg Med*. 2010;17(10): 1048-1054.
28. Uzbay TI. Atypical antipsychotic drugs and ethanol withdrawal syndrome: a review. *Alcohol Alcohol*. 2012; 47(1):33-41.
29. McKeon A, Frye MA, Delanty N. The alcohol withdrawal syndrome. *J Neurol Neurosurg Psychiatry*. 2008;79(8): 854-862.



Statement of Ownership, Management, and Circulation (Requester Publications Only)

1. Publication Title Current Psychiatry		2. Publication Number 1 5 3 7 - 8 2 7 6			3. Filing Date 9/17/12	
4. Issue Frequency Monthly		5. Number of Issues Published Annually 12			6. Annual Subscription Price (\$ any) \$113.00	
7. Complete Mailing Address of Known Office of Publication (Not printer) (Street, city, county, state, and ZIP+4®) Quadrant HealthCom Inc., 7 Century Drive, Suite 302 Parsippany, Morris County, NJ 07054-4609					Contact Person Donna Sickles Telephone (include area code) 973-206-8005	
8. Complete Mailing Address of Headquarters or General Business Office of Publisher (Not printer) 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609						
9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor (Do not leave blank)						
Publisher (Name and complete mailing address) Maroy Holcton, 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609						
Editor (Name and complete mailing address) Jeff Bauer, 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609						
Managing Editor (Name and complete mailing address) N/A						
10. Owner (Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual owner. If the publication is published by a nonprofit organization, give its name and address.)						
Full Name		Complete Mailing Address				
Quadrant HealthCom Inc.		7 Century Drive, Suite 302, Parsippany, NJ 07054-4609				
Quadrant Media Corporation		450 Park Avenue, New York, NY 10022				
11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box <input checked="" type="checkbox"/> None						
Full Name		Complete Mailing Address				
12. Tax Status (For completion by nonprofit organizations authorized to mail at nonprofit rates) (Check one) <input type="checkbox"/> The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes: <input type="checkbox"/> Has Not Changed During Preceding 12 Months <input type="checkbox"/> Has Changed During Preceding 12 Months (Publisher must submit explanation of change with this statement)						

PS Form 3526-R, September 2007 (Page 1 of 3 (Instructions Page 3)) PSN: 7530-29-000-3865 PRIVACY NOTICE: See our privacy policy on www.usps.com

13. Publication Title Current Psychiatry		14. Issue Date for Circulation Data Below September 2012	
15. Extent and Nature of Circulation		Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
a. Total Number of Copies (Net press run)		39,784	39,979
b. Legitimate Paid and/or Requested Distribution (By Mail and Outside the Mail)	(1) Outside County Paid/Requested Mail Subscriptions stated on PS Form 3541. (Include direct written request from recipient, telemarketing and internet requests from recipient, paid subscriptions including nominal rate subscriptions, employer requests, advertiser's proof copies, and exchange copies.)	20,421	20,831
	(2) In-County Paid/Requested Mail Subscriptions stated on PS Form 3541. (Include direct written request from recipient, telemarketing and internet requests from recipient, paid subscriptions including nominal rate subscriptions, employer requests, advertiser's proof copies, and exchange copies.)	-	-
	(3) Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Paid or Requested Distribution Outside USPS®	-	-
	(4) Requested Copies Distributed by Other Mail Classes Through the USPS (e.g. First-Class Mail®)	-	-
c. Total Paid and/or Requested Circulation (Sum of 15b (1), (2), (3), and (4))		20,421	20,831
d. Non-requested Distribution (By Mail and Outside the Mail)	(1) Outside County Non-requested Copies Stated on PS Form 3541 (include Sample copies, Requests Over 3 years old, Requests induced by a Premium, Bulk Sales and Requests including Association Requests, Names obtained from Business Directories, Lists, and other sources)	18,875	18,749
	(2) In-County Non-requested Copies Stated on PS Form 3541 (include Sample copies, Requests Over 3 years old, Requests induced by a Premium, Bulk Sales and Requests including Association Requests, Names obtained from Business Directories, Lists, and other sources)	-	-
	(3) Non-requested Copies Distributed Through the USPS by Other Classes of Mail (e.g. First-Class Mail, Non-requested Copies mailed in excess of 10% Limit mailed at Standard Mail® or Package Services Rates)	-	-
	(4) Non-requested Copies Distributed Outside the Mail (include Pickup Stands, Trade Shows, Street Vendors and Other Sources)	-	-
e. Total Non-requested Distribution (Sum of 15d (1), (2), (3) and (4))		18,875	18,749
f. Total Distribution (Sum of 15c and e)		39,296	39,580
g. Copies not Distributed (See Instructions to Publishers #4, (page #3))		488	399
h. Total (Sum of 15f and g)		39,784	39,979
i. Percent Paid and/or Requested Circulation (15c divided by 1 times 100)		52.0%	52.9%
16. Publication of Statement of Ownership for a Requester Publication is required and will be printed in the issue of this publication. October 2012			
17. Signature and Title of Editor, Publisher, Business Manager, or Owner 			Date 9/17/12

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including civil penalties).

PS Form 3526-R, September 2007 (Page 2 of 3)

Bibliography

Amato L, Minozzi S, Vecchi S, et al. Benzodiazepines for alcohol withdrawal. *Cochrane Database Syst Rev.* 2010;(3):CD005063.

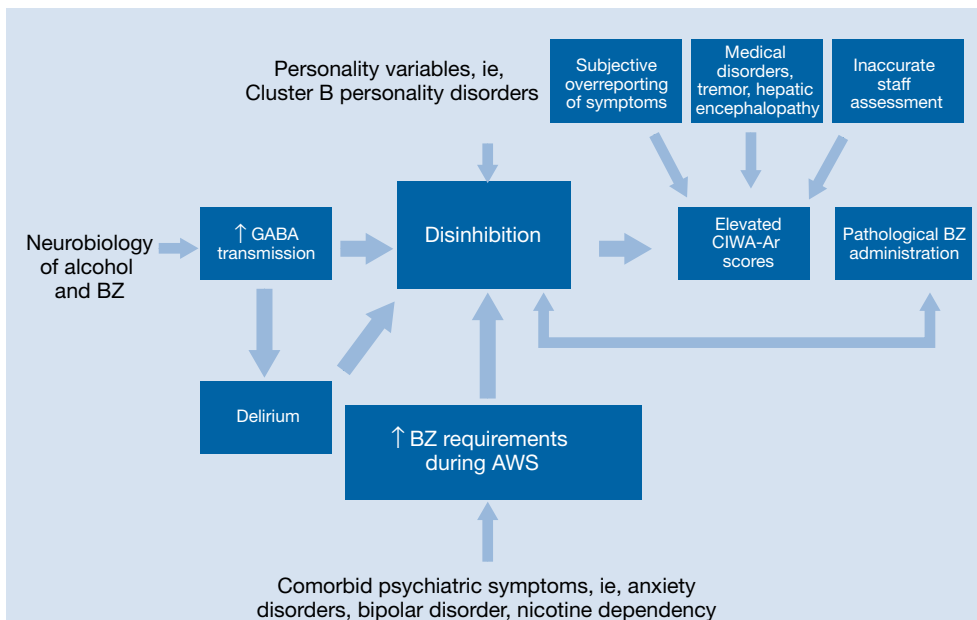
Cassidy EM, O'Sullivan I, Bradshaw P, et al. Symptom-triggered benzodiazepine therapy for alcohol withdrawal syndrome in the emergency department: a comparison with the standard fixed dose benzodiazepine regimen [published online ahead of print October 19, 2011]. *Emerg Med J.* doi: 10.1136/emmermed-2011-200509.

Daeppen JB, Gache P, Landry U, et al. Symptom-triggered vs fixed-schedule doses of benzodiazepine for alcohol withdrawal: a randomized treatment trial. *Arch Intern Med.* 2002;162(10):1117-1121.

DeCarolis DD, Rice KL, Ho L, et al. Symptom-driven lorazepam protocol for treatment of severe alcohol withdrawal delirium in the intensive care unit. *Pharmacotherapy.* 2007;27(4):510-518.

Jaeger TM, Lohr RH, Pankratz VS. Symptom-triggered therapy for alcohol withdrawal syndrome in medical inpatients. *Mayo Clin Proc.* 2001;76(7):695-701.

Weaver MF, Hoffman HJ, Johnson RE, et al. Alcohol withdrawal pharmacotherapy for inpatients with medical comorbidity. *J Addict Dis.* 2006;25(2):17-24.

Figure**Unifying concept for pathological BZ administration during alcohol withdrawal syndrome: Disinhibition**

Although disinhibition has various causes, it may serve as a “final common pathway” that results in excessive benzodiazepine administration caused by a falsely elevated CIWA-Ar score during alcohol detoxification. “Pathological” benzodiazepine administration could further disinhibition and perpetuate the cycle

AWS: alcohol withdrawal syndrome; BZ: benzodiazepine; CIWA-Ar: Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised; GABA: γ -aminobutyric acid

Source: Reference 11