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EDITORIALS

Hospitalists and Alcohol Withdrawal: Yes, Give Benzodiazepines but Is That the Whole Story?

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With 17 million Americans reporting heavy drinking (5 or more drinks on 5 different occasions in the last month) and 1.7 million hospital discharges in 2006 containing at least 1 alcohol-related diagnosis, it would be hard to imagine a hospitalist who does not encounter patients with alcohol abuse.[1,2] Estimates from studies looking at the number of risky drinkers among medical inpatients vary widely—2% to 60%—with more detailed studies suggesting 17% to 25% prevalence.[3–6] Yet despite the large numbers and great costs to the healthcare system, the inpatient treatment of alcohol withdrawal syndrome remains the ''ugly stepsister'' to more exciting topics, such as acute myocardial infarction, pulmonary embolism and procedures.[7,8] We hospitalists typically leave the clinical studies, research, and interest on substance abuse to addiction specialists and psychiatrists, perhaps due to our discomfort with these patients, negative attitudes, or belief that there is nothing new in the treatment of alcohol withdrawal syndrome since Dr Leo Henryk Sternbach discovered benzodiazepines in 1957.[7,9] Many of us just admit the alcoholic patient, check the alcohol-pathway in our order entry system, and stop thinking about it.

But in this day of evidence-based medicine and practice, what is the evidence behind the treatment of alcohol withdrawal, especially in relation to inpatient medicine? Shouldn't we hospitalists be thinking about this question? Hospitalists tend to see 2 types of inpatients with alcohol withdrawal: those solely admitted for withdrawal, and those admitted with active medical issues who then experience alcohol withdrawal. Is there a difference?

The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) defines early alcohol withdrawal as the first 48 hours where there is central nervous system (CNS) stimulation, adrenergic hyperactivity, and the risk of seizures. Late withdrawal, after 48 hours, includes delirium tremens (DTs) and Wernicke's encephalopathy.[10] This is based on studies done in the 1950s, where researchers observed patients as they withdrew from alcohol and took notes.[11,12]

The goal in treatment of alcohol withdrawal is to minimize symptoms and prevent seizures and DTs which, prior to benzodiazepines, had a mortality rate of 5% to 20%. Before the US Food and Drug Administration (FDA) approval of the first benzodiazepine in 1960 (chlordiazepoxide), physicians treated alcohol withdrawal with ethanol, antipsychotics, or paraldehyde.[12] (That is why there is a ''P'' in the mnemonic ''MUDPILES'' for anion gap acidosis.) The first study to show a real benefit from benzodiazepine was published in 1969, when 537 men in a veterans detoxification unit were randomized to chlordiazepoxide (Librium), chlorpromazine (Thorazine), antihistamine, thiamine, or placebo.[12] The primary outcome of DTs and seizures occurred in 10% to 16% of the patients, except for the chlordiazepoxide group where only 2% developed seizures and DTs (there was no *P* value calculated). Further studies published in the 1970s and early 1980s were too small to demonstrate a benefit. A 1997 meta-analysis of all these studies, including the 1969 article,[12] confirmed benzodiazepines statistically reduced seizures and DTs.[13] Which benzodiazepine to use, however, is less clear. Long-acting benzodiazepines with liver clearance (eg, chlordiazepoxide or diazepam) versus short-acting with renal clearance (eg, oxazepam or lorazepam) is debated. While there are many strong opinions among clinicians, the same meta-analysis did not find any difference between them, and a small 2009 study found no difference between a short-acting and long-acting benzodiazepine.[13,14]

How much benzodiazepine to give and how frequently to dose it was looked at in 2 classic studies.[15,16] Both studies demonstrated that symptom-triggered dosing of benzodiazepines, based on the Clinical Institute Withdrawal Assessment (CIWA) scale, performed equally well in terms of clinical outcomes, with less medication required as compared with fixed-dose regimens. Based on these articles, many hospitals created alcohol pathways using solely symptom-triggered dosing.

The CIWA scale is one of multiple rating scales in the assessment of alcohol withdrawal.[17,18] The CIWA-Ar is a modified scale that was designed and validated for clinical use in inpatient detoxification

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centers, and excluded any active medical illness. It has gained popularity, though initial time for staff training and time for administration are limitations to its usefulness. Interestingly, vital signs, which many institutions use in their alcohol withdrawal pathways, were not strongly predictive in the CIWA study of severe withdrawal, seizures, or DTs.[17]

Finally, what about treatment when the patient does develop seizures or DTs? The evidence on how best to treat alcohol withdrawal seizures comes from a 1999 article which demonstrated a benefit of using lorazepam for recurrent seizures.[19,20] Unfortunately, the treatment for DTs is less clear. A 2004 meta-analysis on the treatment of delirium tremens found benzodiazepines better than chlorpromazine (Thorazine), but benzodiazepines versus, or in addition to, newer antipsychotics have not been tested. The amount of benzodiazepine to give in DTs is only a Grade C (ie, expert opinion) recommendation: ''dose for light somnolence.''[21]

All of these studies, however, come back to the basic question: Do they apply to the inpatients that hospitalists care for? A key factor to consider: All of the above-mentioned studies, including the derivation and validation of the CIWA scale, were done in outpatient centers or inpatient detoxification centers. Patients with active medical illness or comorbidities were excluded. This data may be relevant for the patients admitted solely for alcohol withdrawal, but what about the 60 year old with diabetes, coronary artery disease, and chronic obstructive lung disease admitted for pneumonia who starts to withdraw; or the 72-year-old woman who breaks her hip and begins to withdraw on post-op day 2?

There are 6 relatively recent studies that evaluate PRN (as needed) dosing of benzodiazepines on general medical inpatients.[22–27] While ideally these articles should apply to a hospitalist's patients, 2 of the studies excluded anyone with acute medical illness.[24,27] From the remaining 4, what do we learn? Weaver and colleagues did a randomized study on general medical patients and found less lorazepam was given with PRN versus fixed dosing.[26] Unfortunately, the study was not blinded and there were statistically significant protocol errors. Comorbidity data was not given, leaving us to wonder to which inpatients this applies. Repper-DeLisi et al. did a retrospective chart review, after implementing an alcohol pathway (not based on the CIWA scale), and did not find a statistical difference in dosing, length of stay, or delirium.[25] Foy et al. looked at both medical and surgical patients, and dosed benzodiazepines based on an 18-item CIWA scale which included vital signs.[22] They found that the higher score did correlate with risk of developing severe alcohol withdrawal. However, the scale had limitations. Many patients with illness were at higher risk for severe alcohol withdrawal than their score indicated, and some high scores were believed, in part, due to illness. Jeager et al. did a pre-comparison and post-comparison of the implementation of a PRN CIWA protocol by chart review.[23] They found a reduction in delirium in patients treated with PRN dosing, but no different in total benzodiazepine given. Because it was chart review, the authors acknowledge that defining delirium tremens was less reliable, and controlling for comorbidities was difficult. The difficult part of delirium in inpatients with alcohol abuse is that the delirium is not always just from DTs.

Two recent studies raised alarm about using a PRN CIWA pathway on patients.[28,29] A 2008 study found that 52% of patients were inappropriately put on a CIWA sliding scale when they either could not communicate or had not been recently drinking, or both.[29] (The CIWA scale requires the person be able to answer symptom questions and is not applicable to non-drinkers.) In 2005, during the implementation of an alcohol pathway at San Francisco General Hospital, an increase in mortality was noted with a PRN CIWA scale on inpatients.[28]

One of the conundrums for physicians is that whereas alcohol withdrawal has morbidity and mortality risks, benzodiazepine treatment itself has its own risks. Over sedation, respiratory depression, aspiration pneumonia, deconditioning from prolonged sedation, paradoxical agitation and disinhibition are the consequences of the dosing difficulties in alcohol withdrawal. Case reports on ''astronomical'' doses required to treat withdrawal (eg, 1600 mg of lorazepam in a day) raise questions of benzodiazepine resistance.[30] Hence, multiple studies have been done to find alternatives for benzodiazepines. Our European counterparts lead the way in looking at: carbemazepine, gabapentin, gamma-hydroxybuterate, corticotropin-releasing hormone, baclofen, pregabalin, and phenobarbital. Again, the key issue for hospitalists: Are these benzodiazepine alternatives or additives applicable to our patients? These studies are done on outpatients with no concurrent medical illnesses. Yet, logic would suggest that it is the vulnerable hospitalized patients who might benefit the most from reducing the benzodiazepine amount using other agents.

In this issue of the *Journal of Hospital Medicine*, Lyon et al. provide a glimpse into possible ways to reduce the total benzodiazepine dose for general medical inpatients.[31] They randomized inpatients withdrawing from alcohol to baclofen or placebo. Both groups still received PRN lorazepam based on their hospital's CIWA protocol. Prior outpatient studies have shown baclofen benefits patients undergoing alcohol withdrawal and the pathophysiology makes sense; baclofen acts on GABA b receptors. Lyon and collegaues' study results show significant reduction in the amount of benzodiazepine needed with no difference in CIWA scores.[31]

Is this a practice changer? Well, not yet. The numbers in the study are small and this is only 1

institution. These patients had only moderate alcohol withdrawal and the study was not powered to detect outcomes related to prevention of seizures and delirium tremens. However, the authors should be applauded for looking at alcohol withdrawal in medical inpatients.[31] Trying to reduce the harm we cause with our benzodiazepine treatment regimens is a laudable goal. Inpatient alcohol withdrawal, especially for patients with medical comorbidities, is an area ripe for study and certainly deserves to have a spotlight shown on it.

Who better to do this than hospitalists? The Society of Hospital Medicine (SHM) core competency on Alcohol and Drug Withdrawal states, "Hospitalists can lead their institutions in evidence based treatment protocols that improve care, reduce costs- and length of stay, and facilitate better overall outcomes in patients with substance related withdrawal syndromes." [32] Hopefully, Lyon and collegaues' work will lead to the formation of multicenter hospitalist-initiated studies to provide us with the best evidence for the treatment of inpatient alcohol withdrawal on our patients with comorbidities.[31] Given the prevalence and potential severity of alcohol withdrawal in complex inpatients, isn't it time we really knew how to treat them?

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