Improving Care for Inpatient Alcohol Withdrawal Syndrome: Addressing the Lack of Rigorous Research on a Common Condition

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Alcohol withdrawal syndrome (AWS) is common in hospitalized patients—more prevalent than myocardial infarction—and regularly managed by inpatient providers of all disciplines (1). Roughly 95% of patients who experience AWS in the hospital are primarily admitted for other reasons (2–4). Inpatient AWS complicates the care of other conditions, increases the risk of infections and sepsis, and can be fatal (5, 6). In spite of these facts, there has never been a randomized controlled trial evaluating treatments for AWS in hospitalized patients with acute comorbidities. Research guiding inpatient practice has largely been conducted in specialized detoxification units, and a Cochrane review rated only 3% of results from existing randomized controlled trials for AWS as high quality (7). As such, best practices for AWS management in hospitalized and intensive care unit (ICU) patients remain unknown (8).

In this issue of *AnnalsATS*, Bosch and colleagues (pp. 1708–1716) describe a mixed-methods, quasi-experimental study that contributes substantially to our understanding of the strengths and limitations of two commonly used treatments for inpatient AWS: front-loading benzodiazepines and weight-based phenobarbital (9). Many hospitals have adopted symptom-triggered ("CIWA") and front-loading ("Gold/Bellevue") benzodiazepine protocols for AWS based on two high-profile studies (10, 11), but these strategies may pose risks in hospitalized patients. Benzodiazepines have dose-dependent adverse effects, including respiratory depression, delirium, and even death (12). Patients with severe AWS often require very high doses of benzodiazepines because of cross-tolerance between alcohol

and benzodiazepines at the γ-aminobutyric acid (GABA)$_A$ receptor (13, 14). Inpatient providers are thus increasingly using benzodiazepine alternatives for AWS, especially phenobarbital (15–18). Phenobarbital enhances GABA and suppresses glutamate activity in the central nervous system (19). In contrast, benzodiazepines act specifically at the GABA$_A$ receptor to augment GABA signaling but do not address the excess glutamate associated with life-threatening AWS (13, 14, 20). Phenobarbital can control AWS at lower drug concentrations (10–20 mg/dL) than typically required for management of epileptic seizures (20–40 mg/dL) (18, 20, 21). Phenobarbital is also easily administered using weight-based dosing by mouth, intramuscular injection, or intravascular infusion. Based on these perceived advantages, phenobarbital has replaced benzodiazepines as first-line therapy for AWS in some hospital settings (15–18). Unfortunately, similar to practice trends favoring benzodiazepines for AWS in the past, phenobarbital protocols have been implemented for hospitalized patients with AWS in the absence of thorough evaluation.

Bosch and colleagues have conducted the most rigorous implementation study of phenobarbital for inpatient AWS to date and provide insight into a phenomenon happening in hospitals across the country. Prompted by safety concerns regarding the benzodiazepine-based "Gold/Bellevue" (i.e., front-loading) protocol used for severe AWS in their medical ICU (11), the investigators conducted a mixed-methods evaluation of transitioning to a phenobarbital-based protocol. Specifically, they compared processes of care and in-hospital patient outcomes during the final year of the benzodiazepine-based protocol and first year of the phenobarbital-based protocol for AWS in their medical ICU.

Prior studies comparing phenobarbital to benzodiazepine treatment for inpatient AWS have produced inconclusive results. In two studies from a single hospital (17, 18), providers preferentially used phenobarbital in
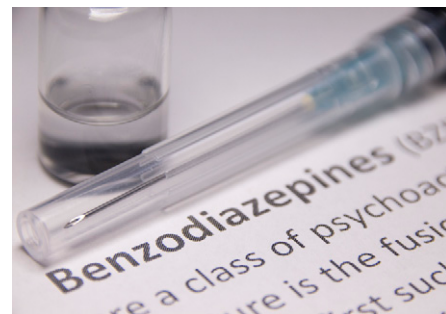
patients with a history of severe or complicated AWS, yet there were no statistically significant differences in rates of AWS-related complications (e.g., mechanical ventilation), mortality, or length of stay among medical and surgical inpatients. A third study compared patients treated with a phenobarbital-based protocol to those treated with a symptom-triggered lorazepam protocol for AWS in an academic medical ICU where providers were free to choose either protocol (16). Patients treated with phenobarbital had significantly shorter ICU and hospital stays, lower incidence of mechanical ventilation, and reduced need for adjunctive medications. However, none of these studies adjusted for severity of AWS or other covariates that might predict these outcomes. Differences between patients whose providers chose to use benzodiazepines versus phenobarbital may have influenced the results (i.e., selection bias). Additional limitations include post hoc retrospective study designs; small, underpowered sample sizes; and differences in the benzodiazepine and phenobarbital treatment protocols used in different studies.

The study by Bosch and colleagues adds meaningfully to the literature in several ways. They compared two AWS protocols, front-loading benzodiazepines and weight-based phenobarbital, implemented during separate, consecutive periods of time in a single medical ICU. This quasi-experimental design limited the influence of selection bias. Using analysis of covariance–based interrupted-time-series analyses, the authors also adjusted for effects of secular trends and

confounding owing to between-group differences. Their qualitative work offers important insights regarding barriers and facilitators to use of each treatment protocol from the perspective of ICU team members. For example, interviews made it clear that the phenobarbital protocol resulted in less need for ongoing consultation between nurses and physicians, freeing up scarce time for other patient care for both groups. The phenobarbital protocol was noninferior to benzodiazepines for the primary safety outcome—monthly rate of mechanical ventilation. Furthermore, the nonsignificant trend favored phenobarbital; the rate of mechanical ventilation postimplementation of phenobarbital was 13% versus 17% during the period of time when patients received the benzodiazepine protocol. Of the seven secondary safety outcomes evaluated, none were significantly worse with the phenobarbital protocol and two were significantly better—physical restraint use (32% vs. 52%) and hospital length of stay (7 vs. 9 d). As more hospitals implement phenobarbital protocols to treat inpatient AWS, Bosch and colleagues' detailed description of their methods, survey instruments, treatment algorithms, etc., provides a rubric for how to rigorously evaluate changes in AWS care protocols pursued in other inpatient settings. Although the single-center design may limit generalizability, the study demonstrates the important role implementation research can play in improving ICU care. The authors' nuanced mixed-methods analyses allow readers to understand how care was modified and whether similar protocol changes could be applicable and worthwhile at their own institutions.

Bosch and colleagues' study is an important step forward for a common inpatient condition that has rarely been the focus of rigorous clinical investigations (8). Yet as a medical community, it is time we do more. This study suggests phenobarbital may be a viable alternative to benzodiazepines, but the question of which agent should be first-line therapy for inpatient AWS remains unanswered. A definitive, high-quality randomized controlled trial comparing the effectiveness of benzodiazepines and phenobarbital for inpatient AWS is needed. ■

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