Barbiturates for the treatment of alcohol withdrawal syndrome: A systematic review of clinical trials

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1. Introduction

Approximately 15% to 20% of hospitalized patients and 50% of trauma patients suffer from alcohol use disorders [1,2]. Many of these patients manifest signs and symptoms of alcohol withdrawal syndrome (AWS) when their alcohol consumption is abruptly stopped or significantly reduced [3,4]. Patients with AWS exhibit a wide array of symptoms including tremor, tachycardia, nausea, insomnia, agitation, hallucination, diaphoresis, or tonic-clonic seizures [2,4]. Alcohol withdrawal delirium, also known as delirium tremens (DTs), is the most severe manifestation of AWS. It is characterized by a fluctuating mental state marked by disturbances of attention and awareness, disorientation, diminished responsiveness, hallucinations, or delusions combined with alcohol withdrawal symptoms [3,5]. About 5% of hospitalized patients with AWS will progress to DTs typically 48 to 72 hours after alcohol cessation [4,6]. The serious complications of AWS such as alcohol withdrawal delirium and seizures often lead to intensive care unit (ICU) admission, prolonged hospital and ICU stay and increased mortality ranging from 5 to 15% [4–7].

Benzodiazepines (BZDs) have been a mainstay of therapy for prevention and treatment of AWS [2,4,6,7]. However, there are limited data available on whether BZDs have definite superiority in managing AWS and its complications when compared with other agents [3]. In addition, some patients with severe AWS may not respond to high doses of BZDs, as they develop tolerance over time due to the γ-aminobutyric acid (GABA) receptor desensitization [4,6,8]. Benzodiazepine-refractory (or resistant) withdrawal symptoms may be described as uncontrolled agitated states despite of the need for ~40 mg of lorazepam (LZP) in the first 3 to 4 hours, but it has not been well defined in the current literature [4,9]. Patients with BZD-refractory withdrawal symptoms are more likely to require continuous BZD infusion, which may result in a higher rate of mechanical ventilation and longer ICU and hospital stays [4,6].

Recently, there has been growing interest in the use of dexmedetomidine as adjunctive therapy to BZDs for the treatment of AWS. Dexmedetomidine, a presynaptic α2-receptor agonist, could be an attractive option particularly in severe AWS patients experiencing respiratory depression from BZD therapy since it does not cause respiratory depression [10]. Studies have suggested that dexmedetomidine as an adjunct in AWS may decrease alcohol withdrawal symptoms and benzodiazepine use, thereby potentially preventing mechanical ventilation [11,12]. However, it should be noted that clinical outcome data of...
trolled trial [10–14]. Additionally, dexmedetomidine therapy is more costly and resource-intensive than other alternatives. As a result, the clinical impact of dexmedetomidine in AWS still remains unclear.

Previous studies have demonstrated the use of barbiturates, GABA receptor agonists similar to BZDs, as an adjunctive to BZD therapy may be effective and safe in severe AWS refractory to BZD [15,16]. Of interest, in such patients, phenobarbital (PB) may play a role in reducing the need for ICU admission as well as mechanical ventilation [15–17].

Intravenous (IV) PB in particular has great potential in the treatment of severe AWS for the following reasons: (1) An IV formulation of PB can be especially useful when treating patients with acute AWS or DT compared to oral drugs, (2) IV PB can suppress acute withdrawal symptoms quickly due to its rapid onset of action (approximately 5 minutes) (3) Patients are less likely to require subsequent oral PB for AWS because PB concentrations gradually decline following IV injections due to its long duration of action (a half-life of 53–140 hours), and (4) From a safety standpoint, PB doses used for the treatment of hypnosedative withdrawal do not produce prominent central nervous system (CNS) depression [18–20]. Therefore, we conducted a systematic review of the current literature to assess the efficacy and safety of barbiturates with or without BZDs versus BZDs for the treatment of AWS in the acute setting. Additionally, the secondary objective was to evaluate the clinical utility and potential of PB in terms of preventing or reducing ICU admission as well as mechanical ventilation in patients developing acute AWS.

2. Materials and methods

2.1. Data sources

We developed a comprehensive list of keywords to identify all relevant studies for inclusion, which included alcohol withdrawal syndrome, alcoholism, alcohol dependence, delirium tremens, barbiturates, and benzodiazepine. A literature search was performed using MEDLINE (1946–July 2015), EMBASE (1947–July 2015), and the Cochrane Library (1992–July 2015). Additionally, a manual review of citations from retrieved articles was performed to capture relevant studies that are not indexed in the electronic bibliographic databases.

2.2. Study selection

Trials were included if they contained all of the following PICOTS (population, intervention, comparison, outcome, timing, and setting and study design) criteria: (1) Studies included inpatients with AWS; (2) Any barbiturates given as a single agent or with other agents were compared to BZDs alone or BZDs in combination with other agents; and (3) Randomized controlled trials, non-randomized controlled trials, and observational studies with comparison groups were included in the final analysis. All other types of clinical trials including case reports and series were excluded. Primary outcomes were total cumulative doses of barbiturates and BZD, duration of delirium, number of seizure episodes, or respiratory and cardiovascular complications. Secondary outcomes included length of ICU and hospital stay.

2.3. Data extraction and synthesis

Two authors (YM, MT) and one professional librarian (EL) independently screened and selected studies for inclusion. Discrepancies were resolved through discussions and consensus. We chose the Mixed Methods Appraisal Tool (MMAT) to evaluate the methodological quality of each study due to the nature of studies included in this review, mixed methods studies [21]. Two independent reviewers (YM, MT) assessed the quality of evidence using the MMAT scoring metrics. An overall quality score for each study was assigned based on the number of criteria met, ranging from 25% (*) to 100% (****). In case of disagreement between the two reviewers, we sought a second opinion from an external person with expertise in drug information/informatics before making the final assessment decision.

3. Results

Our initial screen of titles and abstracts resulted in a total of 98 studies, out of which 29 citations possibly eligible by inspection of abstracts were retrieved for full-text review (Figure). Ultimately, eight articles were retained for final inclusion; however, following the quality appraisal process, one study was excluded from our systematic review due to its small and unbalanced sample size between groups (pre-guideline group, n = 30 vs post-guideline group, n = 3) [22]. A summary of included clinical trials is depicted in Table.

3.1. Randomized controlled trials (RCTs)

In our analysis, we identified three RCTs, including two double-blind trials and one partially double-blind study [16,23,24]. Rosenthal and colleagues published a double-blind, randomized, placebo-controlled trial of PB for the treatment of acute alcohol withdrawal in the emergency department (ED) [16]. A total of 102 patients with a primary admission diagnosis of acute AWS were randomly assigned to receive either a single dose of intravenous (IV) PB (10 mg/kg, n = 51) or placebo (n = 51). In addition to study drugs, all patients were placed on a symptom-triggered LZP protocol for AWS. Baseline characteristics including initial median alcohol withdrawal clinical assessment (AWCA) scores (6 PB vs 7 placebo [mild-moderate withdrawal if AWCA score were between 3 and 10]) were similar in both groups. The authors observed significant decreases in ICU admission rate (8% vs 25%, difference 17% [95% confidence interval (CI) 4–32%]) and use of continuous LZP infusion (4% vs 31%, difference 27% [95% CI 14–41%]) in PB group as compared with placebo group. Furthermore, there were no significant differences in adverse effects including the requirement for intubation or restraints and seizure between the two groups. However, it needs to be acknowledged that decisions on ICU admission and initiation of continuous LZP drip were made solely at the discretion of ED providers.

Results from other two studies demonstrated favorable outcomes of barbiturates in the treatment of AWS, but failed to show superiority of barbiturates over BZDs, especially in regards to controlling alcohol withdrawal (AW) symptoms [23,24]. Of note, these studies compared barbiturates alone with other agents. Kain and colleagues conducted a randomized, partially double-blind trial to evaluate the effectiveness of sodium pentobarbital, chlordiazepoxide, paraldehyde, and phenobarbazine for the treatment of uncomplicated DTs [23]. Patients in the three groups (pentobarbital, n = 46; chlordiazepoxide, n = 46; phenobarbazine, n = 46) initially received intramuscular (IM) injections in a double-blind fashion followed by oral capsules identical in appearance, whereas those in the paraldehyde group (n = 55) were treated with a liquid oral formulation. The authors did not find any significant differences in the duration (P > .2) or severity (P > .1) of AW symptoms among the 4 groups. One of the major drawbacks of this study is that investigators solely relied on the subjective clinical assessments to measure study outcomes.

In Hendey’s study, patients in the ED with acute AW were randomized into two groups: 25 patients were treated with IV PB (a 260-mg dose followed by subsequent doses of 130 mg) and 19 patients received IV LZP (2 mg). In both groups, the timing and number of subsequent doses were up to the treating physicians [24]. This study found no differences in AW symptom control, ED length of stay, hospital admission rates, or 48-hour follow-up Clinical Institute Withdrawal Assessment (CIWA) scores between the two groups. The authors concluded that PB and LZP were similarly effective in ED patients with acute AWS. However, 48-hour follow-up results should be interpreted with caution because only 40% (18/44) patients returned for 48-hour follow-up.
reassessments. In addition, it should be noted that at ED discharge, patients in PB group received oral placebo, whereas patients treated with LZP were given oral chlordiazepoxide.

All 3 studies had small sample sizes, and significant heterogeneity existed among the studies in key components of study methodology—participants, interventions, and outcomes. Nonetheless, in contrast to the two studies using PB alone, Rosenson’s study in which BZDs were administered in combination with PB showed promising results.

3.2. Non-randomized controlled trials

We identified another double-blind comparison trial of barbital versus diazepam in the treatment of DTs, but no clear description of randomization was evident in the study [25]. Patients presenting to a psychiatric hospital with DTs were further categorized into grade 1 to 3 based on the presence of: (1) tremor only; and (2) tremor and hallucination; (3) tremor, hallucination, and disorientation. Ninety-one patients were assigned to receive either diazepam (DZP) IV (n = 44) or barbital PO (n = 47). The global assessment ratings based on the severity and duration of acute state were similar between both groups in patients experiencing grade 1 and 2 DTs, but barbital was superior to diazepam in patients with grade 3 DTs. The authors suggested barbiturates have the potential role as an alternative to BZDs in refractory DTs. However, the results of this study should be carefully interpreted due to the lack of objective outcome measures.

3.3. Cohort study

Three retrospective cohort studies also met our inclusion criteria. One of the major limitations of all three studies is that participants were recruited for a long period of time and allocated to different interventions during different time periods, which could introduce selection bias as clinical practices and patient populations change over time.

Michaelson and colleagues retrospectively collected data on patients with DT from two hospitals (Righospitalet and Bispebjerg Hospital) from January 1998 to December 2006 [26]. The purpose of the study was to compare effectiveness and safety of PB and DZP in the treatment of DTs. At Righospitalet, patients were treated with PB (n = 53) while at Bispebjerg, patients were treated with PB (n = 53) until 2001, and thereafter patients were given DZP because of an institution-wide change in AW treatment regimen (n = 88). Investigators did not find any significant differences in duration of DT, length of hospital stay, as well as respiratory or cardiovascular complications. However, investigators noted that 9% of patients treated with DZP failed to respond to large doses of DZP (mean 1274 ± 632 mg), but their DTs were successfully treated after therapy was changed to PB. It should be also pointed out that carbamazepine (BZD group 41% vs PB groups 2% each) and haloperidol (PB Righospitalet group 28% vs PB Bispebjerg group 32% vs DZP Bispebjerg group 56%) were given to patients in addition to study drugs, which could have confounded the results. Another potential limitation is the lack of objective assessments of AWS.

In a retrospective pre-post study, Duby and colleagues evaluated the effectiveness of protocolized management of AWS, in which escalating BZD dosing regimens (up to 120 mg/dose) were used first and then escalating doses of PB (60 → 120 → 240 mg) were added when patients were still restless and agitated, as compared with non-protocolized care [17]. Patients with AWS admitted to an ICU received either the protocolized treatment (postintervention group, n = 75) or usual (non-protocolized) care (preintervention group, n = 60). The postintervention group was associated with significant reductions in length of ICU stay (5.2 vs 9.6 days, P = .0004), ventilator days (1.31 vs 5.6 days, P < .0001), requirement for mechanical ventilation due to AWS (5% vs 22%, P < .001), BZD use (mean LZD dose 94 mg vs 317 mg, P = .0002) and need for continuous sedation (24% vs 55%, P < .001). Additionally, mean PB doses used in the postintervention group were significantly higher (78 mg vs 50 mg, P = .04); however, it is questionable whether these differences are clinically meaningful since PB was given to very few patients in both groups. Furthermore, one of the limitations of this study is that some important baseline characteristics were notably different between the two groups. Patients in the preintervention group were significantly older (55.7 vs 50.7 years, P = .03) and had the higher SOFA (Sequential organ failure assessment) scores (6.1 vs 3.9, P = .0004) compared with those in the postintervention group.

In a study by Gold et al patients admitted to the ICU for the treatment of AWS were divided into two groups: a prediagnosis group (n = 54, from July 2000 to June 2002) and a postdiagnosis group (n = 41, from July 2003 to May 2005) [15]. Ninety-eight percent of patients had DTs and 34% had AW seizures at the time of inclusion in the study. The updated AWS guidelines, which were implemented in July 2003 at the study institution, included a more aggressive strategy consisting of significant dose escalation of BZDs (up to 150 mg/dose) and combination of PB in case of resistant AWS. Significant increases in total amount of DZP (248 vs 562 mg; P = .001) and PB use (17 vs 58%; P = .01) were found in the prediagnosis group versus the postdiagnosis group,
<table>
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<th>Reference</th>
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<tr>
<td>Kaim et al (1972) [23]</td>
<td>R, C, Partial DB, prospective</td>
<td>N = 46 chlordiazepoxide IM + matching placebo X 10 D N = 46 perphenazine IM + matching placebo X 10 D N = 41 pentobarbital IM + matching placebo X 10 D N = 55 paraldehyde PO X 10 D</td>
<td>Inclusion criteria: DTs (disorientation, tremor, hallucination); male Exclusion criteria: frank schizophrenic reaction; chronic brain syndrome; serious medical or surgical Hx; DM; Dx of epilepsy (not associated with heavy drinking)</td>
<td>Efficacy: duration and severity of the episode from initiation of study drugs to delirium cessation (nurses’ symptom record and physicians’ judgments) Safety: mortality, complications</td>
<td>Goal of Tx: light somnolence or sleep</td>
<td>Mortality: 1 death (unrelated to Tx) Complications: 3 convulsions (1 each in chlordiazepoxide, paraldehyde, and perphenazine groups) Duration of episodes/severity of episodes (milder than average, average, worse than average, or very severe): no significant between-drug differences</td>
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<tr>
<td>Kramp et al (1978) [25]</td>
<td>DB, C, prospective</td>
<td>N = 44 (grade 1, N = 23; grade 2, N = 8; grade 3, N = 13) diazepam 20 mg IM (max 200 mg/d) + placebo PO N = 47 (grade 1, N = 19; grade 2, N = 11; grade 3, N = 17) barbital 500 mg PO (max 5 g/d) + placebo IM</td>
<td>Inclusion criteria: acute AWS (tremor and intense perspiration) Exclusion criteria: intake of psychoactive drugs within 24 h before Tx; alcohol in blood at the time of Tx</td>
<td>Efficacy: (1) Course and duration of acute state (numbers of hours until last and last-but-one dose; total number of doses given; time to sleep, (2) Global assessment (satisfactory or nonsatisfactory) Safety: mortality, complications (seizures)</td>
<td>Grade 1: Tremor (no hallucination) Grade 2: Tremor + hallucination (no disorientation) Grade 3: Tremor + hallucination + disorientation</td>
<td>No pts died; no serious complications (one pt in each group developed a single convulsion) Course and duration of acute state: no marked differences are seen; in grade 2, pts treated with barbital fell asleep earlier than pts treated with diazepam (P &lt; .05) Global assessment: in grade 1 and 2, the effects of Tx were not statistically significant; in grade 3, barbital significantly superior to diazepam (P &lt; .05)</td>
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<td>Gold et al (2007) [15]</td>
<td>Retrospective cohort</td>
<td>N = 41, Postguideline (100% diazepam, Avg total daily dose = 562 mg; 58% phenobarbital) N = 54 preguideline (100% diazepam, Avg total daily dose = 248 mg; 17% phenobarbital) Duration of data collection: preguideline (July 2000-June 2002); postguideline (July 2003-may 2005)</td>
<td>Inclusion criteria: pts admitted to medical ICU solely for Tx of severe AWS Exclusion criteria: presence of a serious medical or surgical diagnosis; evidence of use of other illicit substances Baseline characteristics: DTs (preguideline 98% vs postguideline 98%); AW seizures (preguideline 27% vs postguideline 38%)</td>
<td>Requirement of MV: incidence of nosocomial PNA, ICU LOS</td>
<td>Definition of AWS based on DSM-IV Guidelines: symptom-triggered therapy</td>
<td>Use of MV (postguideline 21.9% vs preguideline 47.3%, P = .008) Total ICU LOS (postguideline 3.8 ± 5.4 vs preguideline 4.5 ± 4.7 days, P not significant) Nosocomial complications (postguideline 30.5% vs preguideline 19.5%, P = .1)</td>
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Both drugs significantly decreased CIWA scores from baseline to ED discharge (phenobarbital 15.0–5.4, P < .0001 vs lorazepam 16.8–4.2, P < .0001); No differences between phenobarbital and lorazepam groups in baseline CIWA scores (P = .3), discharge scores (P = .4), ED LOS (267 min vs 256 min, P = .8), hospital admission rate (12% vs 16%, P = .8), and 48-hour follow-up CIWA scores (P = .6).

Inclusion criteria: a known or suspected case of AW
Exclusion criteria: severe symptoms or altered mental status; significant comorbid medical illness
Change in AW scores from ED baseline score to ED discharge and 48-hr reassessment; ED LOS; hospital admission rates

A trend toward an increase in the frequency of DT per year in group C (A 5.9 ± 1.8 vs B 12.8 ± 4.1 vs C 17.0 ± 8.7, P = .061)
No significant intergroup differences in mortality, DT duration, LOS, ICU admission rate, and complications
9% pts in Group C were resistant to large doses of diazepam
respectively. Furthermore, patients in the postguideline group showed significant reductions in the requirement for mechanical ventilation (47 vs 22%; \(P = .008\)) and trends toward decreases in ICU length of stay and nosocomial infections. This study has several strengths when compared with the studies by Duby and Michaelson. First, the baseline characteristics of participants were similar across the two groups. Second, although the decision to intubate was up to the discretion of the treating physicians, criteria for other outcome measures such as ICU admission were clearly defined and stated.

4. Discussion

A total of 7 studies evaluating the use of barbiturates versus BZDs in the treatment of AWS were included in our analysis. We identified that there is little high-quality evidence available at this time; however, most of studies have a sample size greater than 100 patients and quality ratings using the MMAT of all seven studies were 50 % or higher. Of note, none of these studies demonstrated inferiority of barbiturates to BZDs in the management of AWS. Furthermore, overall safety profiles of barbiturates were comparable to those of BZDs across all studies included in this review.

In our analysis, we found the following trends: (1) Barbiturates combined with BZDs tend to confer a greater benefit to patients with severe forms of alcohol withdrawal than those with mild to moderate AWS; (2) The combination of PB and BZDs may lead to favorable additive clinical effects in controlling alcohol withdrawal symptoms. Additionally, this regimen could be used as a strategy aiming at preventing ICU admission and mechanical ventilation; (3) The use of PB may be a potential option for treating patients with alcohol withdrawal symptoms refractory to high doses of BZDs; and (4) Barbiturates seem to be well tolerated in most patients despite concerns for their low safety margins.

Many studies in our review consistently supported that PB alone or in combination with BZDs was more effective in treating severe or serious AWS compared to BZDs alone [15,16,25,26]. Results from studies by Gold and Michaelson in which most patients had DTs indicated that the use of PB alone or as an adjunct lead to favorable outcomes. Additionally, a double-blind study by Kramp et al found no differences in efficacy and safety outcomes of barbital and DZP in patients with mild to moderate AWS, but barbital appeared to have better effects when patients developed DTs.

Previous studies have proposed that the incidence of mechanical ventilation was quite high in patients with severe AWS especially treated with high doses of BZDs, which then resulting in a higher rate of ICU length of stay and nosocomial pneumonia [15,27]. On basis of our analysis, it seems that PB incorporated into BZD therapy is associated with reduced requirement of mechanical ventilation or ICU admission in severe AWS patients compared to benzodiazepines alone [15–17]. These findings highlight that concomitant use of PB and BZDs in severe AWS could lead to improved outcomes by avoiding mechanical ventilation although further investigation is warranted to elucidate its exact role for this indication.

From the pharmacologic standpoint, barbiturates exhibit additive effects with BZDs on AWS. It can be explained by the fact that barbiturates activate inhibitory GABA-A receptor by prolonging the duration of chloride channel opening, whereas BZDs augment the frequency of channel opening at GABA-A receptors [4,6]. Barbiturates may also provide additional beneficial effect by inhibiting stimulatory N-methyl-D-aspartate (NMDA) receptor, making them more attractive for patients with BZD-refractory AWS [4,6,28]. Clinical findings seem to support the hypothesis of additive effects observed between PB and BZDs. Studies by Gold, Michaelson, Rosenson, and Duby demonstrated positive effects of PB on AWS when it was used as an adjunct to high doses of BZDs [15–17,26].

There have been concerns about the safety of barbiturates in patients with AWS [4,6,9]. Serious complications of PB, which may occur more often in elderly patients or those with impaired liver function, include respiratory depression, over-sedation, and hypotension [8,29]. Dose titration of PB can be challenging because of its narrow margin of safety and long half-life (53 to 140 hours) [4,8,9]. Additionally, there is no antidote for barbiturates available in case of a barbiturate overdose, while flumazenil can be used to reverse the serious adverse effects of BZDs. Nonetheless, barbiturates were well tolerated in all studies included in our analysis. In fact, two studies that included critically ill patients showed that treatment with BZD and PB according to AWS protocols was associated with a significant decrease in need for mechanical ventilation [15,17].

Although our analysis suggests that the use of PB has great potential in the management of AWS, several limitations and directions for future research should be addressed. First, studies published in non-English journals were excluded from our analysis, which may over- or underestimate the efficacy and safety of PB in patients with acute AWS. Second, there is very limited literature available comparing PB with BZDs or BZDs plus PB for the treatment of AWS. One area of future research should focus on confirming the beneficial effect of concomitant PB therapy on reducing the requirement of mechanical ventilation and how its effect translates into improved overall outcomes in severe AWS patients. Third, the assessment tools for alcohol withdrawal were inconsistent. Of seven trials included, three studies did not use any objective measures to assess alcohol withdrawal symptoms. Additionally, the clinical institute withdrawal assessment for alcohol (CIWA) and its variations were used in only three trials. Fourth, different dosing strategies for PB were used in all these studies. It has been suggested that the combination of PB and BZDs can enhance the risk of serious side effects such as central nervous system (CNS) depression and hypotension [30,31]. Clinicians should be also aware that when these agents are given in combination with alcohol, they can further augment the sedative effects of alcohol [32,33]. Thus, special caution should be taken when deciding the dosage regimen of PB, particularly in patients requiring combination therapy for AWS. Finally, it has been hypothesized that the sooner barbiturate was given to patients with AWS, the better symptom control was achieved [34]. None of the studies reviewed in this analysis investigated the association between the timing of PB treatment and outcomes in AWS. In a study by Rosenson, ED patients who were placed on a lorazepam-based alcohol withdrawal protocol received study drugs approximately one hour after the first dose of lorazepam was given [16]. However, it is not certain whether positive outcomes from PB therapy were affected by its prompt administration.

5. Conclusions

Although current clinical applications of this systematic analysis may be limited due to a paucity of evidence from randomized control trials, it is still notable that the use of PB seems particularly promising in its attempt to reduce the need for ICU admission or mechanical ventilation for the treatment of acute AWS. Based on our findings, for the treatment of AWS, we would not recommend PB as the initial agent in place of BZD; however, it is reasonable to use PB as an adjunct to a BZD-based regimen in patients experiencing acute AWS while requiring high BZD doses. The questions as to how PB would be best incorporated into a BZD-based standard regimen in a way that potentially avoid serious negative outcomes associated with AWS such as mechanical ventilation still need to be addressed in clinical trials. Thus, large-scale, well-designed clinical trials are warranted to evaluate the definitive role of PB in the treatment of AWS.

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