Alcohol and Alcoholism, 2015, 50(5) 509–518
doi: 10.1093/alcalc/agv043
Advance Access Publication Date: 21 May 2015
Article

Article

Prospective Validation Study of the Prediction of Alcohol Withdrawal Severity Scale (PAWSS) in Medically Ill Inpatients: A New Scale for the Prediction of Complicated Alcohol Withdrawal Syndrome

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Received 27 September 2014; Revised 25 March 2015; Accepted 26 March 2015

Abstract

Aims: The prevalence of alcohol use disorders (AUDs) among hospitalized medically ill patients exceeds 40%. Most AUD patients experience uncomplicated alcohol withdrawal syndrome (AWS), requiring only supportive medical intervention, while complicated AWS occurs in up to 20% of cases (i.e. seizures, delirium tremens). We aimed to prospectively test and validate the Prediction of Alcohol Withdrawal Severity Scale (PAWSS), a new tool to identify patients at risk for developing complicated AWS, in medically ill hospitalized patients.

Methods: We prospectively considered all subjects hospitalized to selected general medicine and surgery units over a 12-month period. Participants were assessed independently and blindly on a daily basis with PAWSS, Clinical Institute Withdrawal Assessment—Alcohol, Revised (CIWA-Ar) and clinical monitoring throughout their admission to determine the presence and severity of AWS.

Results: Four hundred and three patients were enrolled in the study. Patients were grouped by PAWSS score: Group A (PAWSS < 4; considered at low risk for complicated AWS); Group B (PAWSS ≥ 4; considered at high risk for complicated AWS). The results of this study suggest that, using a PAWSS cutoff of 4, the tool's sensitivity for identifying complicated AWS is 93.1% (95%CI[77.2, 99.2%]), specificity is 99.5% (95%CI[98.1, 99.9%]), positive predictive value is 93.1% and negative predictive value is 99.5%; and has excellent inter-rater reliability with Lin's concordance coefficient of 0.963 (95% CI [0.936, 0.979]).

Conclusion: PAWSS has excellent psychometric characteristics and predictive value among medically ill hospitalized patients, helping clinicians identify those at risk for complicated AWS and allowing for prevention and timely treatment of complicated AWS.

INTRODUCTION

Alcohol use disorders (AUDs) are reported in 10–32% of hospitalized medical patients (Nielsen *et al.*, 1994; Smothers *et al.*, 2004; Dolman and Hawkes, 2005; Doering-Silveira *et al.*, 2014), and as many as 45% of patients visiting a primary care practitioner (Buchsbaum *et al.*, 1992). The prevalence of AUD is higher in some specialized inpatient units, affecting about 40% of patients presenting to the emergency department (Holt *et al.*, 1980); 42% of hospitalized veterans (Tracy *et al.*, 2004); up to 44% of elderly inpatients admitted to acute geriatric units (Henni *et al.*, 2013); 43–81% of head and neck surgical patients (Moore *et al.*, 1989; Nielsen *et al.*, 1994; Martin *et al.*, 2002); up to 60% of intensive care unit (ICU) patients (Awissi *et al.*, 2013) and 59–67% of trauma patients (Herve *et al.*, 1986; Soderstrom *et al.*, 1992; Gentilello *et al.*, 1995; Spies *et al.*, 1996a; Angles *et al.*, 2008; Pandharipande *et al.*, 2008). However, a recent meta-analysis of 39 studies revealed that most healthcare professionals have considerable difficulty with the identification of problem drinking in clinical practice, identifying under half of those with AUD based on clinical judgment and correctly recording AUD in the notes in only about 30% of cases (Mitchell *et al.*, 2012). This meta-analysis corroborates the findings described by others (Buchsbaum *et al.*, 1992).

A hospital admission may result in an abrupt cessation of alcohol consumption (i.e. enforced abstinence) for individuals with AUD and thus provide a risk period for alcohol withdrawal syndrome (AWS). Even though the majority of patients at risk of AWS will develop only minor or uncomplicated withdrawal symptoms (e.g. tremors, diaphoresis, irritability, insomnia, some elevation in vital signs indicating increased adrenergic activity) (Victor and Adams, 1953; Turner *et al.*, 1989), up to 20% of patients develop symptoms associated with complicated AWS, including withdrawal seizures and delirium tremens (DT) (Saitz and O'Malley, 1997; McKeon *et al.*, 2008; Maldonado *et al.*, 2010). Alcohol withdrawal related seizures occur in about 5–17% of patients experiencing active AWS (Victor and Adams, 1953; Victor and Brausch, 1967; Schuckit *et al.*, 1995; Mennecier *et al.*, 2008). DT occurs in 10% of patients with AWS (Yost, 1996), and may result in death in up to 20% of cases with certain medical comorbidities (Hemmingsen *et al.*, 1979; Holloway *et al.*, 1984; Cushman, 1987; Horstmann *et al.*, 1989; Schuckit *et al.*, 1995; Erwin *et al.*, 1998; Monte *et al.*, 2010; Campos *et al.*, 2011).

Complicated AWS is associated with increased in-hospital morbidity and mortality, increased lengths of stay, inflated costs of care, increased burden and frustration of nursing and medical staff and worsened cognitive functioning. It has been reported that AWS among ICU patients is associated with a 2-fold mortality (Stanley *et al.*, 2003; Moss and Burnham, 2006). In addition to the life-threatening complications of AWS, the rate of hospital morbidity and mortality due to infections, cardiopulmonary insufficiency or bleeding disorders is 2–4 times greater in chronic alcoholics (Herve *et al.*, 1986; Jensen *et al.*, 1988; Jurkovich *et al.*, 1993; Spies *et al.*, 1996a,b; Moller and Tonnesen, 1999; Spies and Rommelspacher, 1999). Moreover, studies have demonstrated that experiencing complicated AWS is detrimental to the central nervous system, causing neuronal degeneration and death (Rose *et al.*, 2010). Thus, appropriate identification and prevention of complicated AWS in subjects at risk can greatly benefit patients by reducing length of hospital stay, medical comorbidities and even the risk of brain damage.

In about 80% of cases, the symptoms of uncomplicated alcohol withdrawal do not require aggressive medical intervention and usually disappear within 2–7 days of the last drink (Victor and Adams, 1953). As a result, unnecessary prophylaxis or treatment with benzodiazepine and other agents facilitating Gamma-Aminobutyric Acid (GABA) transmission in patients feared to be at risk of AWS but only experiencing uncomplicated AWS may lead to a number of unintended consequences including excessive sedation, falls, respiratory depression and medication-induced delirium (Johnson, 1961; Maldonado, 2008; 2010; Maldonado *et al.*, 2010). Due to lack of any similar previously existing tools, we developed the Prediction of Alcohol Withdrawal Severity Scale (PAWSS) (Maldonado *et al.*, 2014). Given the tool's excellent psychometric properties in a small pilot study, we herein evaluate its validity in a larger population.

Development of PAWSS

Even though there are several tools that allow clinicians to quantify the severity of ongoing AWS [e.g. Clinical Institute Withdrawal Assessment—Alcohol, Revised (CIWA-Ar)] (Sullivan *et al.*, 1989), to date no tool has been validated to identify those medically ill patients at risk of AWS; thus missing the opportunity for prophylaxis, prevention and timely intervention (Maldonado, 2010). Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati *et al.*, 2009; Moher *et al.*, 2009) we conducted a systematic literature search, including PubMed, PsychInfo, MEDLINE and Cochrane Databases, for evidence-based clinical factors associated with the development of AWS (Maldonado *et al.*, 2014). The 10 most common factors identified were used to develop the PAWSS (Fig. 1), in order to assist in the identification of medically ill patients at risk for complicated AWS (i.e. alcohol withdrawal seizures and DT) (Maldonado *et al.*, 2014). The results of a pilot study ($n = 69$) conducted among inpatients admitted to a general medicine unit over a 2-week period demonstrated excellent sensitivity and specificity of the PAWSS for prediction of complicated AWS in this population (Maldonado *et al.*, 2014).

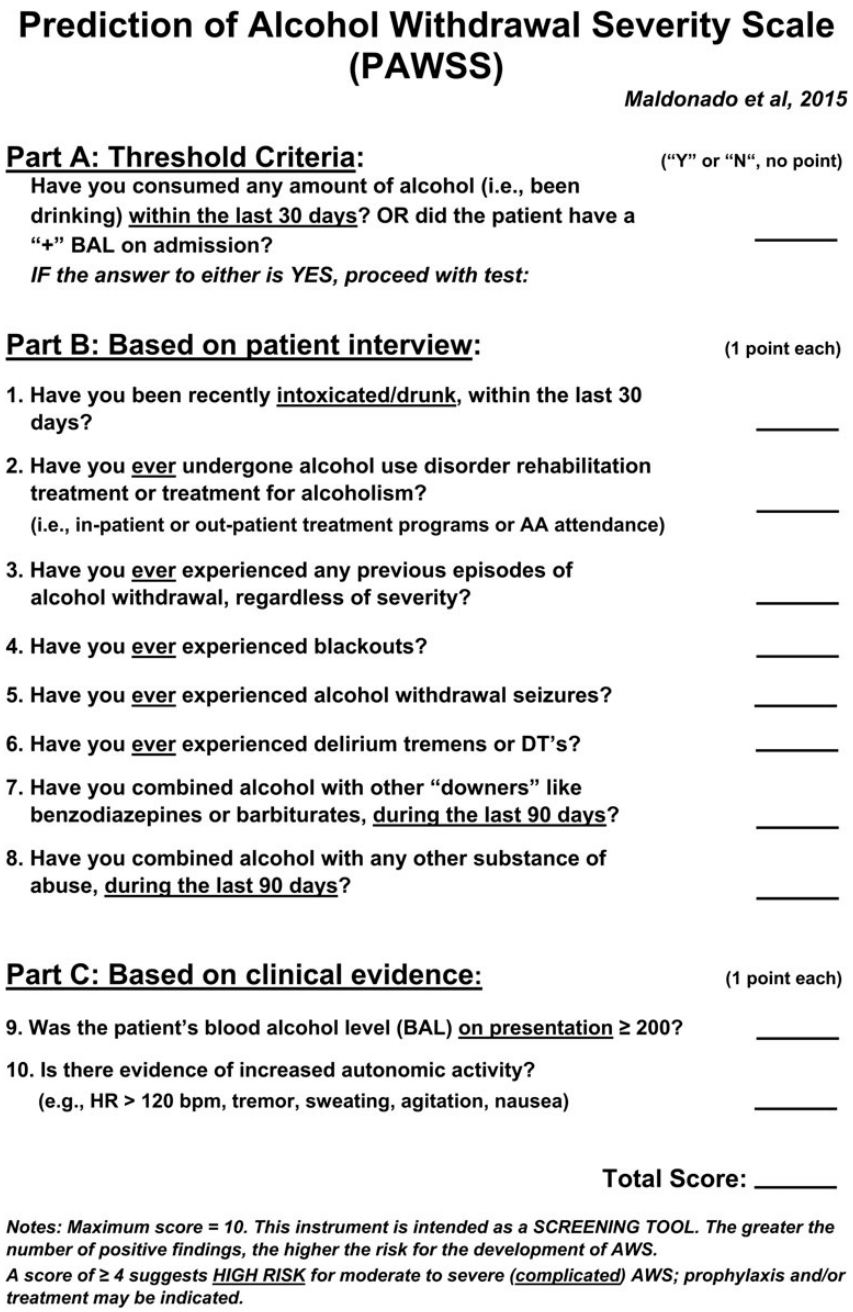
METHODS

Study setting and participants

After obtaining authorization from our institution's Institutional Review Board (IRB), we proceeded to conduct a large, prospective trial of medically ill patients, hospitalized in the general internal medicine and surgery wards at Stanford University Medical Center between May 2012 and April 2013 to test PAWSS' validity and reliability in detecting medically ill inpatients at risk for complicated AWS. All patients admitted over the previous 24 h were identified using daily hospital admission logs on the participating medical unit. These patients were approached and consented for participation in the study.

Inclusion and exclusion criteria

Inclusion criteria included any patient directly admitted to participating general medicine and surgery units from the Emergency Department, out-patient clinics or community setting (e.g. directly admitted from a physician's office or patient's home) within the previous 24 h, or transferred from other in-hospital medical units within 48 h of admission; 18+ years of age, able to communicate in English; and willing and able to consent to participate in the study. Exclusion criteria included patients transferred from outside inpatient medical facilities, given that the time course of symptoms and possible administration of pharmacological interventions (for either prophylaxis or management) could not be reliably identified as these factors could affect the course and presentation of AWS; patients with imminent discharge



Prediction of Alcohol Withdrawal Severity Scale (PAWSS)

Maldonado et al, 2015

Part A: Threshold Criteria: ("Y" or "N", no point)

Have you consumed any amount of alcohol (i.e., been drinking) within the last 30 days? OR did the patient have a "+" BAL on admission? _____

IF the answer to either is YES, proceed with test:

Part B: Based on patient interview: (1 point each)

1. Have you been recently intoxicated/drunk, within the last 30 days? _____
2. Have you ever undergone alcohol use disorder rehabilitation treatment or treatment for alcoholism? (i.e., in-patient or out-patient treatment programs or AA attendance) _____
3. Have you ever experienced any previous episodes of alcohol withdrawal, regardless of severity? _____
4. Have you ever experienced blackouts? _____
5. Have you ever experienced alcohol withdrawal seizures? _____
6. Have you ever experienced delirium tremens or DT's? _____
7. Have you combined alcohol with other "downers" like benzodiazepines or barbiturates, during the last 90 days? _____
8. Have you combined alcohol with any other substance of abuse, during the last 90 days? _____

Part C: Based on clinical evidence: (1 point each)

9. Was the patient's blood alcohol level (BAL) on presentation ≥ 200? _____
10. Is there evidence of increased autonomic activity? (e.g., HR > 120 bpm, tremor, sweating, agitation, nausea) _____

Total Score: _____

Notes: Maximum score = 10. This instrument is intended as a SCREENING TOOL. The greater the number of positive findings, the higher the risk for the development of AWS.
A score of ≥ 4 suggests HIGH RISK for moderate to severe (complicated) AWS; prophylaxis and/or treatment may be indicated.

Fig. 1. Prediction of Alcohol Withdrawal Severity Scale (PAWSS) tool.

plan (i.e. not expected to remain in the hospital for at least 48 h after enrollment into the study); patients with an active, uncontrolled seizure disorder; patients in active, severe alcohol withdrawal (as defined by a CIWA-Ar score ≥20) (Sullivan *et al.*, 1989); patients unable to understand the PAWSS questionnaire (e.g. unable to understand English) and patients unable (e.g. too sedated, comatose, cognitively impaired) or unwilling to consent for the study. The primary teams were allowed to identify subjects they believed to be inappropriate to participate in the study due to the severity of their medical condition (e.g. too sick to participate) or extreme circumstances (e.g. moribund). To provide unbiased data in the analysis, all patients were included regardless of probable or confirmed alcohol use.

Study design

Patients who provided consent were then followed by the research team for a maximum of 3 days, unless they were discharged earlier, in addition to receiving standard medical care. Day 1 included informed consent process and the one-time administration of PAWSS by a member of the research team blinded to the patient's clinical characteristics and the results of other research tools (See Fig. 1 for PAWSS tool) (Maldonado *et al.*, 2014).

On days 1, 2 and 3, all patients were assessed with the CIWA-Ar (Sullivan *et al.*, 1989) every 8 h by their nurse, and with the Alcohol Withdrawal Severity Scale (AWS scale) (Wetterling *et al.*, 1997) twice a day by a member of the research team, again blinded to the results of all other assessments. As per hospital protocol, if any patient

developed AWS symptoms, CIWA-Ar assessments were performed more frequent in order to allow for close monitoring of the patient's response to treatment. Participants discharged before day 3 were assessed with the CIWA-Ar by telephone on day 3.

The primary teams were not informed of PAWSS or AWS scale results, although they were aware of the patient's alcohol use history and CIWA-Ar scores, as per our institution's standards of care. Patients who developed signs of AWS (as indicated by CIWA-Ar and/or defined by clinical assessment), or who arrived to the hospital in active withdrawal, were managed by their primary team and received standard care. All clinical notes, medications, autonomic functioning measures, CIWA-Ar, AWS scale scores and other data pertaining to the absence or presence of AWS according to DSM-IV-TR criteria were collected, along with other variables from the medical chart [i.e. blood alcohol concentration (BAC) levels if collected, laboratory values, medications].

For our study, as widely accepted in the literature, we defined uncomplicated alcohol withdrawal as a patient meeting DSM-IV-TR criteria (APA, 2000) for alcohol withdrawal with mild symptoms or having a CIWA-Ar score <15 (Sullivan *et al.*, 1989; Sellers *et al.*, 1991; Etherington, 1996). Similarly, complicated withdrawal was defined as a patient meeting DSM-IV-TR criteria for alcohol withdrawal with moderate or severe symptoms or having moderate or severe alcohol withdrawal symptoms as indicated by a CIWA-Ar score ≥15 (Sullivan *et al.*, 1989), including the presence of symptoms severe enough for the primary team to administer barbiturate or benzodiazepine agents (Foy *et al.*, 1988; Mayo-Smith, 1997; Mennecier *et al.*, 2008). A transition from uncomplicated to complicated AWS has been associated with a higher risk of complications such as confusion, seizures and hallucinations in those untreated (Foy *et al.*, 1988; Mayo-Smith, 1997).

Outcomes

The primary outcomes for this study consist of the PAWSS' ability in predicting complicated AWS, in regards to its sensitivity, specificity, positive and negative predictive values (NPVs), as well as inter-rater reliability. Secondary outcomes include differences between demographic characteristics of patients with high and low PAWSS scores.

Statistical analysis

Demographic data for the sample were summarized as age means, gender and ethnicity proportions, as well as percentages of primary medical and comorbid psychiatric diagnoses. Z–ratios were calculated to test for any differences between patients with 'positive' PAWSS score (≥4) and patients with negative PAWSS score (<4); t–tests were performed to test for the differences between the means. Initial PAWSS assessments were conducted by two independent members of the research team, blinded to each other's results; Cohen's Kappa and Lin's concordance coefficients were calculated to evaluate the tool's inter-rater reliability in a random sample of 49 patients.

In the original pilot study we found a 6% incidence of complicated AWS in our specific population of medically ill individuals (Maldonado *et al.*, 2014). This was similar to previous samples of patients admitted to a general hospital (Foy and Kay, 1995). Therefore, we extrapolated from the results of our previous study and assumed that complicated delirium would occur in 6% of subjects. Given these assumptions, we calculated that 400 subjects would provide >80% power to find a significant difference between groups with low and high PAWSS scores given a two-sided alpha level of 0.05 using the 'Java applets for power and sample size' computer software program (Lenth, 2007,2006–2009).

A PAWSS of 4 was used as the cutoff point for the prediction of complicated AWS as determined by the original pilot study (Maldonado *et al.*, 2014). The scale's quality (i.e. specificity and sensitivity) and efficiency [i.e. positive predictive value [PPV], NPV] were calculated using the same PAWSS cutoff of 4, actual outcome (i.e. development of complicated AWS) and the occurrence of false positive and negative diagnoses. A receiver operating characteristic (ROC) analysis and the Quality Receiver Operating Characteristic (QROC) were calculated to re-evaluate PAWSS's optimal cutoff score for maximum sensitivity and specificity and to test the scale's performance; these values were confirmed using a logistic regression model (Kraemer, 1992a,b), using PAWSS scores as the independent variable and the actual development of complicated AWS as the dependent variable.

RESULTS

During the study period, a total of 1533 subjects were admitted to the participating medical and surgical wards. Figure 2 shows a detailed flow of the study's recruitment. A total of 409 patients who met inclusion criteria were approached and consented to participate in the study; 6 cases had to be removed from analysis due to unavailable initial PAWSS assessments, leading to our final analysis sample of $N = 403$.

Table 1 describes sample demographics, with roughly 50% of the subjects being male, and largely Caucasian, reflective of our medical center's demographics. There was a significant statistical difference in age between positive and negative PAWSS outcome groups ($P = 0.0002$).

Table 2 describes the most common medical diagnoses prompting hospitalization for the study sample. Table 3 lists patients' reported primary psychiatric disorders as documented by the primary team in their admissions' notes, based on prior available history or patients' self-report. As noted, patients with positive PAWSS scores were much more likely to have documented, by the primary team, any psychiatric or substance abuse disorder, mood disorder or AUD on admission.

Inter-rater reliability was measured in two ways: treating PAWSS scores as binary or continuous variables. When PAWSS scores were treated as binary measures, either indicating high risk for complicated withdrawal (PAWSS ≥ 4) or not (PAWSS < 4), the Cohen's Kappa coefficient was found to be 1, indicating perfect agreement. This reflects 42 cases of agreement on deeming patient as low risk, 7 cases of agreement of deeming patient as high risk and no cases of disagreement. When PAWSS scores were treated as a continuous outcome, Lin's concordance coefficient was found to be 0.963 (two-sided 95% Confidence Interval [CI] [0.936, 0.979]), indicating moderate to substantial agreement. While raters disagreed on few items on several patients, these disagreements did not change the subject's AWS risk categories in any of the patients assessed (e.g. risk for uncomplicated versus complicated AWS).

Of the 403 participants with full data, 374 obtained a PAWSS score less than the cutoff (<4). A total of 29 subjects obtained a 'positive' PAWSS score (≥4). The average PAWSS score for patients with positive score was 6.28 (standard deviation [SD] 1.53, range 4–8). Table 4 provides percentages of individual PAWSS items positive among this high risk group. Of the 374 subjects predicted to not be at risk, 372 never experienced complicated AWS. Thus we encountered two false negative cases. Neither patient experienced seizures,

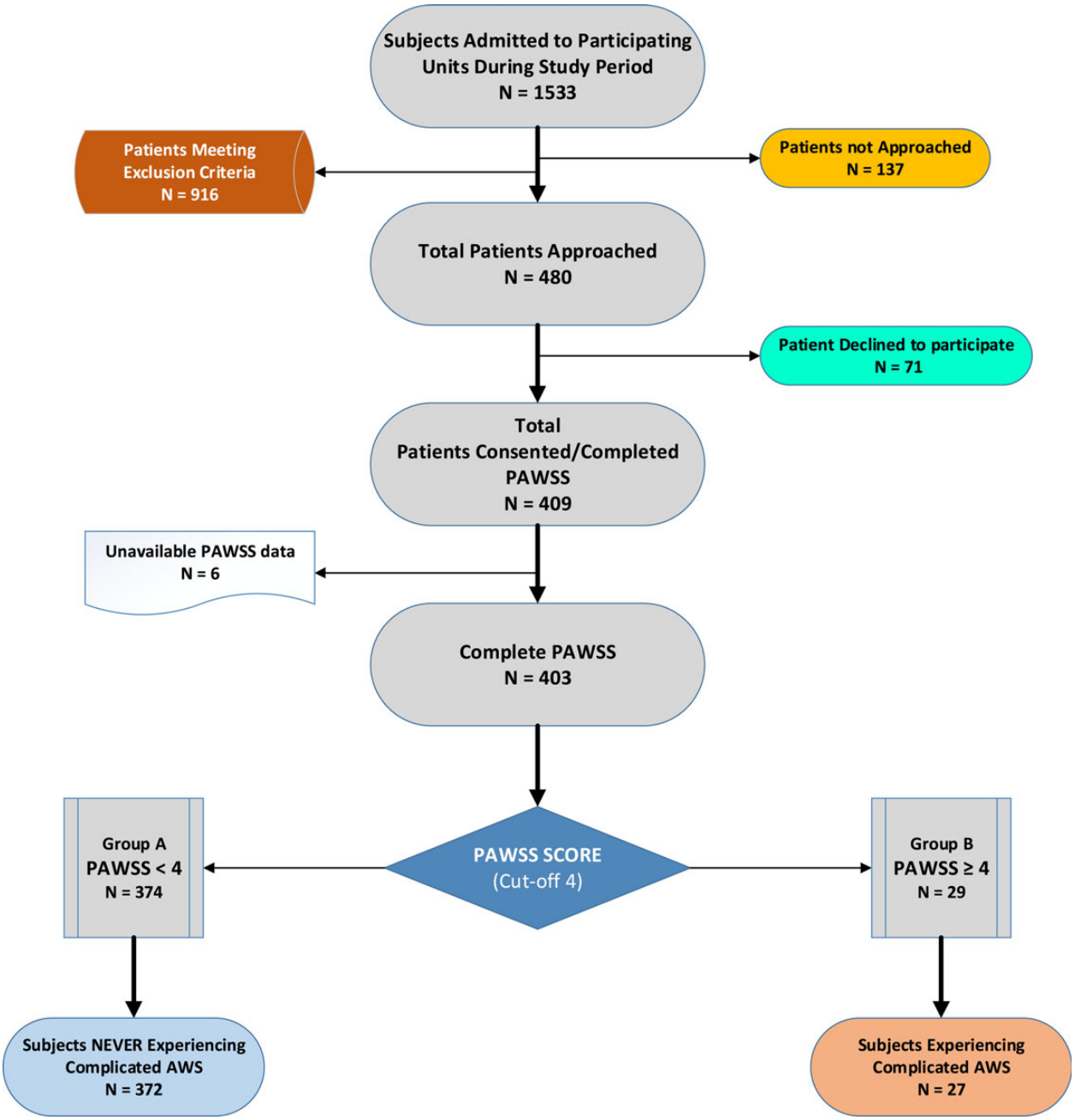


Fig. 2. Flow chart of patient recruitment.

Table 1. Demographic data

Demographic variables	Patient groups			Statistical significance between PAWSS groups
	Total ($N = 403$)	Negative PAWSS (<4): ($N = 374$)	Positive PAWSS (≥4): ($N = 29$)	
Age in years, average (SD)	61.5 (17.4)	62.4 (17.4)	49.3 (11.8)	$P = 0.0002$
Gender (% male)	55.3%	54.6%	65.5%	NS
Ethnicity (%)	Caucasian 68.0%	Caucasian 66.6%	Caucasian 86.2%	NS
	African American 8.9%	African American 9.1%	African American 6.9%	
	Latino 6.2%	Latino 6.1%	Latino 6.9%	
	Asian 7.7%	Asian 8.6%	Asian 0%	
	Others 9.2%	Others 9.6%	Others 0%	

PAWSS, Prediction of Alcohol Withdrawal Severity Scale; NS, not significant; SD, standard deviation.

Table 2. Sample's primary admission diagnosis

Primary diagnoses (completed PAWSS)	*N*	%
Abdominal (e.g. cirrhosis, pancreatitis, gastroenteritis, cholangitis, mesenteric ischemia, Crohn's/ulcerative colitis, *C. difficile* colitis, gastrointestinal bleeding, abdominal pain)	76	19
Respiratory (e.g. pneumonia, pulmonary embolism, COPD exacerbation, pleural effusion, amyotrophic lateral sclerosis)	83	21
Cardiovascular (e.g. CHF, hypotension, syncope)	96	24
Infectious, other than abdominal and respiratory (e.g. bacteremia, sepsis, cellulitis, graft infection)	38	9
Hematologic (e.g. anemia, neutropenia, DVT)	12	3
Neuropsychiatric [other than alcohol withdrawal] (e.g. seizure disorder, head trauma, meningitis, migraine, neuralgia, suicidal attempt, neuropathic pain and other pain syndromes)	22	5
AWS[a]	17	4
Musculoskeletal (e.g. hip pain/fracture, rhabdomyolysis)	20	5
Other (e.g. anaphylaxis, dehydration, hematuria, hyponatremia, neck mass, rectal prolapse)	39	10
Total	403	100

AWS, alcohol withdrawal syndrome; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombosis.

[a]Patients with primary diagnoses of AWS were enrolled in the study only if their CIWA-Ar scores on admission were ≥20, consistent with the study's inclusion and exclusion criteria.

Table 3. Primary psychiatric comorbid diagnosis as per primary team[a]

Primary psychiatric comorbidity	Total (*N* = 403)	Negative PAWSS (<4): (*N* = 374)	Positive PAWSS (≥4): (*N* = 29)	Statistical significance between PAWSS groups (*P*)
None	295 (73.2%)	288 (77.0%)	7 (24.1%)	<0.0001
Mood disorders	74 (18.4%)	60 (16.0%)	14 (48.3%)	<0.0001
Anxiety disorders	12 (3.0%)	10 (2.7%)	2 (6.9%)	0.197
Psychotic disorders/others	5 (1.2%)	3 (0.8%)	2 (6.9%)	0.0043
Substance use disorder, other than alcohol	6 (1.5%)	4 (1.1%)	2 (6.9%)	0.0126
Alcohol use disorder	7 (1.7%)	5 (1.3%)	2 (6.9%)	0.0126
Any substance or alcohol use disorder	13 (3.2%)	9 (2.4%)	4 (13.8%)	0.0008
Any psychiatric disorder	108 (26.8%)	86 (23.0%)	22 (75.9%)	<0.0001

[a]Psychiatric disorders were elicited by primary teams either from prior documentation in the chart or from patients' self-reports.

Table 4. Percentages of positive individual PAWSS items among the 29 patients with positive (≥4) PAWSS scores; items presented in the decreasing order of percentages

PAWSS item number	Item description	Percentage of item present in positive PAWSS group
1	Recent intoxication (within the last 30 days)	93.1
3	Ever experienced previous AWS	86.2
2	Ever undergone alcohol use disorder rehabilitation treatment	75.9
4	Ever experienced blackout	75.6
6	Ever experienced delirium tremens (DT)	72.4
10	Evidence of increased autonomic activity	65.5
5	Ever experienced alcohol withdrawal seizures	58.6
9	BAC > 200[a]	37.9
7	Combined with other CNS depressant agents ('downers') in last 90 days	31.0
8	Combined with any other substances in last 90 days	27.6

AWS, alcohol withdrawal syndrome; BAC, blood alcohol concentration; CNS, central nervous system; PAWSS, Prediction of Alcohol Withdrawal Severity Scale.

[a]BAC was available in 75.8% of this high risk sample.

but both required pharmacological management for complicated withdrawal symptoms. On the other hand, of the 29 subjects predicted to be at high risk (i.e. PAWSS ≥ 4), 27 experienced symptoms consistent with complicated AWS requiring pharmacological management. Thus, we encountered two false positive cases. A detailed analysis demonstrates that the PAWSS has a 93.1% sensitivity (95% CI

Table 5. Calculation of specificity, sensitivity, PPV and NPV

	AWS '+' *N*	AWS '–' *N*	Total *N*
PAWSS '+'	True positives (TP) 27	False positives (FP) 2	All PAWSS '+' 29
PAWSS '–'	False negatives (FN) 2	True negatives (TN) 372	All PAWSS '–' 374
Total	Patients with AWS (AWS '+') 29	Patients with no AWS (AWS '–') 374	Total patients 403

Notes: When using PAWSS score cutoff of ≥ 4: Sensitivity = TP / (TP + FN) x 100% = 93.1% (95% CI [77.2, 99.2]) Specificity = TN / (TN + FP) x 100% = 99.5% (95% CI [98.1, 99.9]) PPV = TP / (TP + FP) x 100% = 93.1% (95% CI [77.2, 99.2]) NPV: TN / (TN + FN) x 100% = 99.5% (95% CI [98.1, 99.9])

AWS, Alcohol Withdrawal Syndrome; AWS '+', presence of complicated AWS; AWS '–', no presence of complicated AWS; PAWSS, Prediction of Alcohol Withdrawal Severity Scale; PAWSS '+', PAWSS score of ≥4; PAWSS '–', PAWSS score of <4; TP, True Positive; FP, False positive; TN, True Negative; FN, False Negative; N, number of subjects per group; PPV, Positive Predictive Value; NPV, Negative Predictive Value.

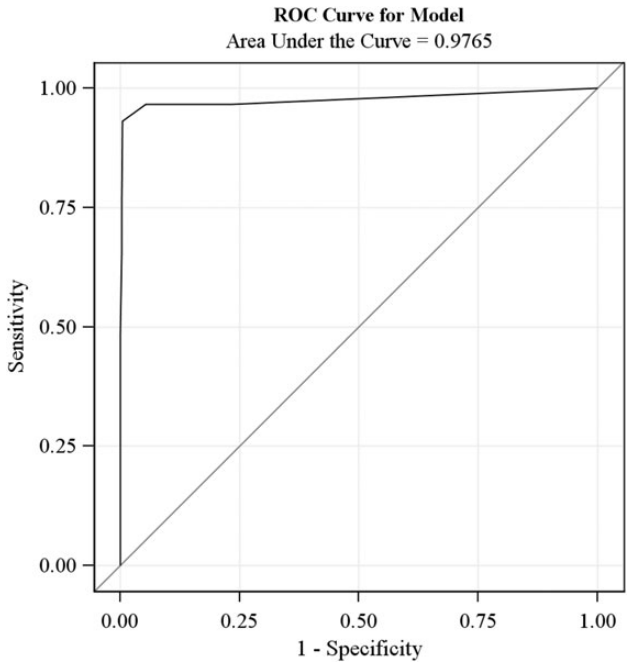


Fig. 3. Receiver operating characteristic analysis for best PAWSS cutoff. ROC, Receiver Operating Characteristic; QROC, Quality Receiver Operating Characteristic; The QROC on *N* = 403 confirms that PAWSS ≥ 4 is the best cutoff point.

[77.2, 99.2]) and a 99.5% specificity (95% CI [98.1, 99.9%]); with a PPV of 93.1% (95% CI [77.2, 99.2]) and a NPV of 99.5% (95% CI [98.1, 99.9%]) (See Table 5).

Of note, only 17 of 27 patients who had positive PAWSS scores and indeed had complicated AWS ('true positives') (63.0%) were also identified by their primary teams being at high risk for AWS (as documented in their own History and Physical admission note) and only 11 patients (40.7%) were treated prophylactically.

Table 6. Sensitivity and specificity report for ROC and QROC analysis

Cutoff	Sensitivity	Specificity	Quality of specificity k (0, 0)	Quality of efficiency k (0.5, 0)	Weighted Kappa coefficient quality of sensitivity k (1, 0)
≥1	0.966	0.767	0.185	0.310	0.952
≥2	0.966	0.872	0.319	0.479	0.958
≥3	0.966	0.947	0.551	0.700	0.961
≥4	**0.931**	**0.995**	**0.926**	**0.926**	**0.926**
≥5	0.759	0.997	0.953	0.836	0.744
≥6	0.655	0.997	0.946	0.761	0.637
≥7	0.483	1.000	1.000	0.634	0.464
≥8	0.310	1.000	1.000	−9.900	0.295

The optimally efficient cutoff point is indicated in bold and is based on a weighted average of the sensitivity and specificity quality indices. QROC analysis confirms that PAWSS ≥4 is the best cutoff point where the highest weighted kappa coefficient/efficiency quality index is 0.926.

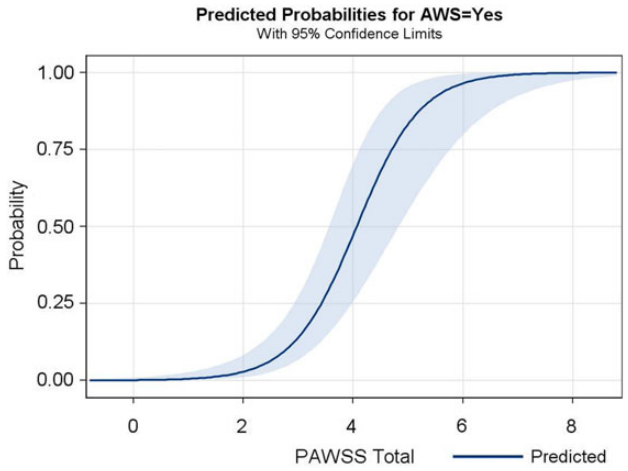


Fig. 4. Logistic regression probability curve. AWS, Alcohol Withdrawal Syndrome; PAWSS, Prediction of Alcohol Withdrawal Severity Scale.

A ROC and QROC analyses supported previous finding based on the original pilot study that a PAWSS score of '4' is the cutoff point with optimal psychometric characteristics (Maldonado *et al.*, 2014). See Fig. 3 for the ROC analysis curve. The results demonstrate an area under the curve (AUC) = 0.9765. Similarly, Table 6 (QROC analysis) compares the tool's sensitivity, specificity and various cutoff points confirming that a PAWSS score ≥4 has the best specificity and sensitivity, as indicated by the highest weighted kappa coefficient 0.926. The best test depends not on the sensitivity and specificity, but on the quality of these indices. So the highest weighted kappa coefficient 0.926 indicates the best cutoff (Kraemer, 1992a). Finally, Fig. 4 shows a logistic regression model, again confirming a PAWSS score ≥4 as the best predictor for complicated AWS. The logistic regression model predicts that at PAWSS = 4, there is a 50/50 chance of AWS; while at PAWSS = 3 it is 13.9% and at PAWSS = 5 it is 83.3% (See Fig. 4).

The administration of PAWSS was not associated with any study-related adverse events.

DISCUSSION

The results of this prospective study demonstrate that the PAWSS has excellent psychometric characteristics and predictive value of complicated alcohol withdrawal among medically ill hospitalized patients. Given the relatively large number of medically ill patients experiencing excessive or uncontrolled drinking and thus the risk for potential development of withdrawal syndromes, the use of tools such as PAWSS adds to the quality of care of hospitalized patients.

Even though multiple tools exist to determine patients experiencing at risk drinking behavior (e.g. CAGE questionnaire, AUDIT) their use allows for referral to addiction services, but does not help predict which patients are at high risk for complicated withdrawal. Similarly, while several tools exist to monitor ongoing alcohol withdrawal symptoms, no tool exists to predict risk of complicated versus uncomplicated withdrawal prior to occurrence of symptoms. Most patients with AUD experience only mild or uncomplicated withdrawal symptoms. Therefore, the identification of those at low risk for complicated AWS allows physicians to monitor the patient's symptoms and provide symptomatic relief, while avoiding the unnecessary use of GABAergic agents which may be associated with a number of unintended but often unavoidable consequences, such as over sedation, excessive falls, disinhibition, respiratory depression, propofol infusion syndrome, propylene glycol toxicity and medication-induced delirium.

On the other hand, the use of PAWSS may allow for the early identification of those at risk of complicated withdrawal and thus help physicians know when aggressive treatment of withdrawal symptoms is imperative. Better yet, it may allow for the implementation of prophylactic management, even before symptoms of complicated withdrawal have started. Timely prophylaxis is important as studies have shown: AWS is associated with neuronal damage, seen as early as 24-hours after experiencing alcohol withdrawal; AWS-induced potentiation of hippocampal neuronal loss, which is later associated with poorer memory performance; kindling effect leads to an increasing risk and severity of future AWS episodes and that an increasing number of alcohol withdrawal episodes negatively affect emotional and cognitive functioning and learning. The available data suggests that even though it is important to timely treat AWS once symptoms occurs, that it is even more important to prevent the development of complicated AWS in order to minimize its long-term detrimental effects.

We propose that use of the PAWSS will help clinicians identify those at risk for complicated AWS and allow them to initiate prophylactic treatment for those at high risk. Preventive and timely intervention should minimize the potential detrimental consequences of complicated AWS and potentially minimize kindling and recidivism of AUD.

Of interest, in our sample, only 63% of the patients predicted to be at high risk for complicated withdrawal by PAWSS were recognized to be at such risk by their primary teams with regular clinical interview and assessment. Moreover, more than half of the patients predicted by PAWSS to be at high risk for complicated withdrawal were only treated after the development of complicated withdrawal symptoms. Thus, we would argue that the use of PAWSS as part of the routine clinical practice and risk assessment could tremendously improve clinician's ability to estimate the risk of complicated alcohol withdrawal, expedite treatment (or better yet, allow for prophylactic intervention) and improve patient outcomes.

While some studies of selected alcohol-dependent patients have found older age to be a risk factor for complicated withdrawal (Hillemacher *et al.*, 2012), others have found younger age to be a risk factor for complicated AWS (Ramos *et al.*, 2013); while others found no association between age and complicated AWS (Rathlev *et al.*, 2000; Lee *et al.*, 2005; Mennecier *et al.*, 2008). In our sample, patients with positive PAWSS were significantly younger than those who had negative PAWSS (average age 49.3 years for those with positive PAWSS versus average age 62.4 for those with negative PAWSS; $P = 0.0002$). However age does not confound the relationship between PAWSS and AWS. We added age to the ROC model and found that the optimal predictor of AWS continues to be PAWSS score of 4 and above, and no significant age cutoffs were identified. Further if we split the sample by median age, and further, split the sample by the median age for those who are AWS positive, the ROC results still indicate that PAWSS ≥ 4 is the optimal cutoff. Of note, this mirrors the finding in our smaller pilot study conducted in similar population (Maldonado *et al.*, 2014). This might indicate that in a large medical center, with overall low prevalence of alcohol withdrawal, younger age might serve as an additional risk factor for complicated AWS. The cause for this finding is not clear, although several reasons might be proposed, including much shorter survival among patients with AUD (Black *et al.*, 1998). For example a recent study supported that patients with AUD die 24–28 years earlier than patients in general population (Westman *et al.*, 2015). Moreover, we could postulate that younger AUD patients may consume greater amounts of alcohol or that these patients were less prepared for a potential hospital admission, thus allowing for greater severity of withdrawal.

Limitations

One limitation of this study was that some patients were independently suspected by their primary teams to be at high risk for complicated withdrawal on admission (usually based on their previous experience with AWS upon admission), and were prophylactically treated for withdrawal by the primary team, and thereby never experienced the full symptom assortment of complicated alcohol withdrawal. In our analysis, if these patients met criteria for a positive PAWSS, independently ascertained in blind fashion apart from the primary team's assessment, and were prophylactically treated, they were counted as having complicated AWS. Of course, the ideal study would not allow for prophylactic treatment for AWS even for patients at very high risk, thus waiting for emergence of AWS and clinical confirmation of the tool's predictability. However, this option is clinically unwise and ethically unacceptable given we have ample evidence of the serious detrimental effects of AWS. Allowing patients to experience AWS just to confirm the tool's validity would have placed patients at significant risk of complications, including seizures, DTs and increased mortality.

Our study had two false positive and two false negative cases. Chart review of the two false negative patients easily revealed that these patients met the risk factors for complicated AWS as presented in PAWSS. The adjusted PAWSS scores were 6 (instead of 0 as obtained by the research personnel) and 4 (instead of 3), respectively. The first patient provided false negative responses to all PAWSS items to the research assistant (RA), thus the recorded PAWSS score '0'. But a cursory retrospective review of his electronic medical records (EMR) revealed significant historical elements translating into a PAWSS score of 6. In fact, this patient was recognized as 'high risk' by the primary team based on clinical and historical data and was prophylactically treated. The second patient admitted to alcohol use, but denied drug use to the RA. Again, a retrospective EMR review confirmed his urine toxicology screen was positive for marijuana, making his revised PAWSS score 4. The PAWSS was designed as a tool based on patients' self-report of alcohol intake and history, as

literature suggests that interviews by clinicians can provide the single most accurate information on alcohol use and relapse when compared to collateral information or selected laboratory data (e.g. BAC) (Cherpitel *et al.*, 2007; Dimartini and Dew, 2012,2013). The experience of this larger study confirms that when used as designed (i.e. patient questionnaire) PAWSS has excellent sensitivity and specificity (as described above); yet, using information provided by both the patient and EMR review could increase the tool's sensitivity to 100%.

While the overall sample size was generous, the relatively low prevalence of complicated AWS in this sample was another limitation. This led to a small number of true positives in the analysis of the data. Future studies should involve a larger data set, across multiple medical settings (e.g. surgical, trauma patients) and populations at higher risk (e.g. veterans administration, inner city hospital) to confirm PAWSS′ ability to predict AWS in every population of medically ill patients.

Finally, this study was completed in medically ill inpatients mostly on general medical floors. Although there were some trauma and surgical patients in our sample, they did not represent the majority. For greater generalizability, the study should be repeated in emergency room patients, purely surgical populations, critical care patients, psychiatric inpatients and patients in detoxification centers, as well as an out-patient sample.

CONCLUSIONS

PAWSS has excellent psychometric characteristics and predictive value among medically ill hospitalized patients, helping clinicians identify those at risk for complicated AWS and allowing for prevention and timely treatment of complicated AWS.

ACKNOWLEDGMENTS

The members of the research team wish to thank the nursing managers, educators and staff of the Stanford Hospital and Clinics B2, B3 and C2 inpatient units, with whom their professionalism, collaboration and excellence in patient care made this work possible. The authors also want to thank Heavenly Swendsen and Shengchun Wang, Ph.D. for their invaluable assistance in the screening and recruitment of patients and collection of data. We would also like to extend our sincere appreciation to all the patients involved in this study.

FUNDING

This study was funded in part by a generous unrestricted contribution of the Chase Research Fund.

CONFLICT OF INTEREST STATEMENT

The authors disclosed no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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