The "Prediction of Alcohol Withdrawal Severity Scale" (PAWSS): Systematic literature review and pilot study of a new scale for the prediction of complicated alcohol withdrawal syndrome

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ABSTRACT

Background: To date, no screening tools for alcohol withdrawal syndromes (AWS) have been validated in the medically ill. Although several tools quantify the severity of AWS (e.g., Clinical Institute Withdrawal Assessment for Alcohol [CIWA]), none identify subjects at risk of AWS, thus missing the opportunity for timely prophylaxis. Moreover, there are no validated tools for the prediction of complicated (i.e., moderate to severe) AWS in the medically ill.

Objectives: Our goals were (1) to conduct a systematic review of the published literature on AWS to identify clinical factors associated with the development of AWS, (2) to use the identified factors to develop a tool for the prediction of alcohol withdrawal among patients at risk, and (3) to conduct a pilot study to assess the validity of the tool.

Methods: For the creation of the Prediction of Alcohol Withdrawal Severity Scale (PAWSS), we conducted a systematic literature search using PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines for clinical factors associated with the development of AWS, using PubMed, PsychInfo, MEDLINE, and Cochrane Databases. Eligibility criteria included: (i) manuscripts dealing with human subjects, age 18 years or older, (ii) manuscripts directly addressing descriptions of AWS or its predisposing factors, including case reports, naturalistic case descriptions, and all types of clinical trials (e.g., randomized, single-blind, or open label studies), (iii) manuscripts describing characteristics of alcohol use disorder (AUD), and (iv) manuscripts dealing with animal data (which were considered only if they directly dealt with variables described in humans). Obtained data were used to develop the Prediction of Alcohol Withdrawal Severity Scale, in order to assist in the identification of patients at risk for complicated AWS.

A pilot study was conducted to assess the new tool's psychometric qualities on patients admitted to a general inpatient medicine unit over a 2-week period, who agreed to participate in the study. Blind to PAWSS results, a separate group of researchers retrospectively examined the medical records for evidence of AWS.

Results: The search produced 2802 articles describing factors potentially associated with increased risk for AWS, increased severity of withdrawal symptoms, and potential characteristics differentiating subjects with various forms of AWS. Of these, 446 articles met inclusion criteria and underwent further scrutiny, yielding a total of 233 unique articles describing factors predictive of AWS. A total of 10 items were identified as correlated with complicated AWS (i.e., withdrawal hallucinosis, withdrawal-related seizures, and delirium tremens) and used to construct the PAWSS. During the pilot study, a total of 68

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subjects underwent evaluation with PAWSS. In this pilot sample the sensitivity, specificity, and positive and negative predictive values of PAWSS were 100%, using the threshold score of 4.

Discussion: The results of the literature search identified 10 items which may be correlated with risk for complicated AWS. These items were assembled into a tool to assist in the identification of patients at risk: PAWSS. The results of this pilot study suggest that PAWSS may be useful in identifying risk of complicated AWS in medically ill, hospitalized individuals. PAWSS is the first validated tool for the prediction of severe AWS in the medically ill and its use may aid in the early identification of patients at risk for complicated AWS, allowing for prophylaxis against AWS before severe alcohol withdrawal syndromes develop.

Background

Alcohol use disorder (AUD) is the most serious substance abuse problem in the United States; the lifetime prevalence in the general population of alcohol abuse is 17.8%, and of dependence is 12.5% (Grant et al., 2004; Lieber, 1995; Williams et al., 1996). In 2011, 52% of Americans reported current alcohol use, 22.6% participated in binge drinking, and 6.2% reported heavy drinking (SAMHSA, 2012). The problem of AUD is often missed by house officers and may worsen among the growing population of elderly patients. When compared to standardized screening (e.g., CAGE questionnaire, Short Michigan Alcohol Screening Test), about 60% of screen-positive young patients with AUD were identified by their house officers, but only 37% of elderly patients were so identified ($p < 0.05$) (Curtis, Geller, Stokes, Levine, & Moore, 1989).

Although AUD has been reported in 20%–42% of hospitalized medical patients, only about 7% of them are identified by a physician (Dawson, Dadheech, Speroff, Smith, & Schubert, 1992; Dolman & Hawkes, 2005; Gerke, Hapke, Rumpf, & John, 1997; Jarman & Kellett, 1979; Mayo-Smith, 1997; McCusker, Cherubin, & Zimberg, 1971; Moore, 1971; Moore et al., 1989; Nielsen, Storgaard, Moesgaard, & Gluud, 1994; Smothers, Yahr, & Ruhl, 2004; Taylor, Kilbane, Passmore, & Davies, 1986). The prevalence of AUD is higher in specialized populations, affecting about 40% of patients presenting to the emergency department (Holt et al., 1980), 43–81% of head and neck surgical patients (Martin et al., 2002; Moore et al., 1989; Nielsen et al., 1994), 42% of hospitalized veterans (Tracy, Trafton, & Humphreys, 2004), 59–67% of trauma patients (Angles et al., 2008; Gentilello, Donovan, Dunn, & Rivara, 1995; Hervè, Gaillard, Roujas, & Huguenard, 1986; Pandharipande et al., 2008; Soderstrom et al., 1992; Spies, Neuner, et al., 1996), up to 44% of elderly inpatients admitted to acute geriatric units (Henni, Bideau, Routon, Berrut, & Cholet, 2013), and up to 60% of ICU patients (Awissi, Lebrun, Coursin, Riker, & Skrobik, 2013).

AWS includes a broad spectrum of symptoms and severity (Alpert, 1985; Babb & Jenkins, 1990; Batel, 1999; Bayard, McIntyre, Hill, & Woodside, 2004; Berard, 1994; Boeckh, 1980; Bovim, Fauske, & Strandjord, 1987; Brown, 1982; Carlson et al., 2012; Cocayne, 1978; Couzigou & Ledinghen, 2002; Croissant & Mann, 2000; Eastes, 2010; Farfán Sedano et al., 1997; Ferrey & Sicot, 1982; Feuerlein, 1972, 1974; Gillman & Lichtigfeld, 1997; Gippini Pérez, Rodríguez López, Torre Carballada, Tomé y Martínez de Rituerto, & Barrio Gómez, 1990; Goldstein, 1986; Gross, Rosenblatt, Malenowski, Broman, & Lewis, 1972; Hall & Zador, 1997; Heil, Martens, & Eyrich, 1990; Iwasaki, 1988; Johnson, 1961; Kalant, 1977; Landers, 1983; Lerner & Fallon, 1985; Maldonado, 2010; Maldonado, DiMartini, & Owen, 2010; Margolis, Ypinazar, Clough, & Hunter, 2008; Matz, 1997; McElroy, 1981; McKeon, Frye, & Delanty, 2008; McKinley, 2005; McMicken, 1990; Nichols, 1967; Pearson, 1813; Picatoste Merino, 1997; Powell & Minick, 1988; Puz & Stokes, 2005; Rico Irles, 1990; Robertson & Sellers, 1978; Sarff & Gold, 2010; Strasen, 1982; Sutton, 1813; Trucco, 1974; Turner, Lichstein, Peden, Busher, & Waivers, 1989; Victor, 1970; Wooddell,

1979; Yost, 1996; Zilker, 1999). Complicated AWS can present in various forms, including alcohol withdrawal seizures, alcoholic hallucinosis, and delirium tremens (DT). DT constitutes the most severe form of AWS, occurring in 5–10% of patients with AWS (Holt et al., 1980; Victor & Adams, 1953). When left untreated, DT may be fatal in up to 15% of cases (Lee et al., 2005; Thompson, 1978; Thompson, Johnson, & Maddrey, 1975). Even when treated, DT results in death in 1% of cases and in up to 20% of cases in the medically ill, with certain comorbidities (Ferguson, Suelzer, Eckert, Zhou, & Dittus, 1996; Maldonado, 2010; Thompson, 1978; Victor, 1970).

Nevertheless, studies have shown that in medically ill, hospitalized subjects (i.e., not a specialized detoxification or substance abuse unit), most cases of AWS are relatively mild and require only symptomatic management (e.g., mild anxiety, agitation, tremors, nervousness, irritability, insomnia, GI symptoms) (Whitfield et al., 1978). In fact, most patients with AUD experience only uncomplicated or mild withdrawal symptoms (Victor & Adams, 1953). In most cases, the symptoms of mild alcohol withdrawal do not require medical intervention and usually disappear within 2–7 days of the last drink (Hall & Zador, 1997; Schuckit, 2009). Furthermore, studies suggest that the incidence of AWS, among alcohol-dependent subjects admitted to a general medical hospital severe enough to require pharmacological treatment, is between 5 and 20% (Benzer, 1990; Feldman, Pattison, Sobell, Graham, & Sobell, 1975; Foy, McKay, Bertram, & Sadler, 2006; Manasco, Chang, Larriviere, Hamm, & Glass, 2012; Mennecier et al., 2008; Neundörfer, Claus, & Burkowski, 1984; Palmstierna, 2001; Saitz & O'Malley, 1997; Schuckit, Tipp, Reich, Hesselbrock, & Bucholz, 1995; Victor & Adams, 1953). The unnecessary prophylaxis or treatment of patients feared to be at risk of AWS or experiencing AWS may lead to a number of unintended consequences including excessive sedation, falls, respiratory depression, propylene glycol toxicity, disinhibition, and delirium (Busch & Frings, 1988; DeCarolis, Rice, Ho, Willenbring, & Cassaro, 2007; Höjer, Baehrendtz, & Gustafsson, 1989; Kraemer, Conigliaro, & Saitz, 1999; Lejoyeux, Solomon, & Adès, 1998; Malcolm, 2003; de Wit, Jones, Sessler, Zilberberg, & Weaver, 2010). Some have found that delirium may be a significant potential complication of treatment of presumptive AWS (Pandharipande et al., 2006; Repper-DeLisi et al., 2008).

Yet, when complicated (i.e., moderate to severe) AWS do occur, it increases in-hospital morbidity and mortality, prolongs hospital stays, inflates costs, increases the burden on nursing and medical staff, and further worsens cognitive functioning among subjects experiencing withdrawal. For example, among adult patients undergoing head and neck cancer surgery, the development of AWS was associated with an increased incidence of acute medical and surgical complications, length of hospitalization, and hospital-related costs (Genther & Gourin, 2012). Similarly, among those admitted to a level I trauma center, patients experiencing AWS had more ventilator days, intensive care unit days, and total hospital days, suffered more medical complications, and incurred higher care costs (Bard et al., 2006; O'Brien et al., 2007; Spies, Nordman, et al.,

1996). In medically ill patients, alcohol-use disorders and withdrawal increased the need for and duration of mechanical ventilation, development of infections, sepsis, and mortality (de Wit et al., 2010). There is a positive correlation between the severity and duration of delirium tremens symptoms and the occurrence of pneumonia, coronary heart disease, alcohol liver disease, and anemia (Wojnar et al., 1999b).

Moreover, animal and human studies have demonstrated that alcohol withdrawal is detrimental to the central nervous system because it causes neuronal degeneration and death (Kalant, 1977; Rose, Shaw, Prendergast, & Little, 2010). Animal studies show that alcohol withdrawal potentiates loss of hippocampal and cerebellar neurons. Also, in dependent human subjects, subsequent withdrawal episodes are associated with poorer memory performance (Glenn, Parsons, Sinha, & Stevens, 1988; Madeira, Sousa, Lieberman, & Paula-Barbosa, 1993; Paula-Barbosa , Brandão, Madeira, & Cadete-Leite, 1993; Phillips & Cragg, 1984).

Studies of human cortical neurons found that neuronal damage was seen 24 h after experiencing alcohol withdrawal (Nagy, Müller, & László, 2001). Others have demonstrated evidence of increased breakdown of old synapses (i.e., increased concentrations of synaptic membrane protein D2 in CSF) and a decreased selectivity of blood-CSF-barrier permeability to proteins (i.e., IgG, albumin, and alpha 2-macroglobulin) during the process of readaptation to the alcohol-free state (Jørgensen, Hemmingsen, Kramp, & Rafaelsen, 1980). Others have demonstrated impaired cerebral auto-regulation among patients experiencing AWS, as evidenced by all parameters of dynamic cerebral auto-regulation (dCA) ($p < 0.038$) and cerebral blood flow velocity (CBFV) ($p < 0.05$), and have found a strong association between autonomic dysfunction and impaired auto-regulation ($p < 0.001$) (Jochum, Reinhard, Boettger, Piater, & Bär, 2010). These findings suggest that the autonomic dysfunction associated with AWS may increase the risk for cerebrovascular disease among patients experiencing AWS. Studies have confirmed that the risk of mortality was higher in a cohort of patients with severe AWS when compared to a matched control group, even after adjusting for age, sex, and smoking (hazard ratio 12.7; 95% CI 9.1–17.6; $p < 0.001$), and that a standardized mortality ratio in patients with AWS was 8.6 (95% CI 7.7–9.7) (Campos, Roca, Gude, & Gonzalez-Quintela, 2011).

An increasing number of alcohol withdrawal episodes negatively affects emotional and cognitive functioning and learning (Duka et al., 2004). Chronic alcohol consumption may lead to the development of alcohol-related brain damage (ARBD) on human brain structure and function, even in the absence of more discrete and well-characterized neurological concomitants of alcoholism such as Wernicke's encephalopathy and/or Korsakoff syndrome (Zahr, Kaufman, & Harper, 2011).

There is substantial evidence demonstrating that each episode of withdrawal worsens the severity and consequences of the next one, leading to a vicious cycle (Babor & Higgins-Biddle, 2000; Booth & Blow, 1993; Brown, Anton, Malcolm, & Ballenger, 1988; Duka et al., 2004; Lechtenberg & Worner, 1990). There is no doubt that AWS-prophylaxis is the key to the prevention of complications and progression to seizures and frank DT (Erwin, Williams, & Speir, 1998). Therefore, it is imperative that clinicians have a reliable tool to help identify those patients at risk for complicated AWS in order to avoid its associated significant detrimental adverse medical and cognitive consequences; yet, we do not want to unnecessarily overtreat those at low risk due to concern with secondary complications and side effects.

Rationale for the development of a prediction tool

Given the prevalence of alcohol abuse among the hospitalized population, the rate of under-diagnosis (Bostwick & Seaman, 2004; Hopkins, Zarro, & McCarter, 1994) and associated medical complications (Maldonado, 2010), as well as neurocognitive risks associated with the development of AWS, an effective, quick, and standardized method for identifying patients at risk is needed. While there have been attempts to use standardized tools to quantify the severity of AWS, no currently available tools predict which patients will experience the most severe or complicated symptoms, for whom prophylaxis may be indicated.

The Clinical Institute Withdrawal Assessment for Alcohol (CIWA) Scale is the most widely used tool for clinical diagnosis of AWS based on observations of the rater and patient reporting (Puz & Stokes, 2005; Sullivan, Sykora, Schneiderman, Naranjo, & Sellers, 1989). CIWA was originally designed as a tool in alcohol withdrawal research and has been validated only in mild-to-moderate withdrawal and then only in a select population of patients (Daeppen et al., 2002; Jaeger, Lohr, & Pankratz, 2001; Saitz et al., 1994). Studies that have evaluated CIWA frequently have excluded patients with seizures, one of the first signs of severe withdrawal (Saitz et al., 1994; Saitz, Friedman, & Mayo-Smith, 1995). In addition, CIWA does not incorporate vital sign assessment, which can be important in recognizing severe AWS, such as delirium tremens (Monte, Rabuñal, Casariego, Bal, & Pértega, 2009; Salum, 1975; Sankoff, Taub, & Mintzer, 2013). The scale is used to determine the severity of the withdrawal symptoms as they are actively experienced, but does not predict which patients are at risk for withdrawal. Once CIWA is elevated or "positive," the patient is already experiencing withdrawal symptoms and thus an opportunity for AWS prophylaxis has been lost. Moreover, alcohol withdrawal seizures occur early and can develop without preceding autonomic instability or elevations in measures of withdrawal severity scores (e.g., before CIWA is "positive"). Some studies have demonstrated that nearly 20% of alcohol-dependent subjects may experience severe AWS (i.e., seizures or delirium) before prevention measures could be initiated (Foy, Kay, & Taylor, 1997).

The Alcohol Use Disorders Identification Test (AUDIT) was studied as a predictive tool for development of AWS (Babor, Higgins-Biddle, Saunders, & Monteiro, 2001). A prospective study of medical inpatients screened with the AUDIT found that a score ≥8 had a positive predictive value (PPV) of 17.3%. The PPV increased to 47.1% when combined with at least two abnormal biological markers (i.e., GGT, AST, ALT, MCV) (Dolman & Hawkes, 2005). Although the "AUDIT-plus" successfully identified all patients going through withdrawal, it overestimated the risk, and if used as a prediction tool it would have led to half of the patients receiving prophylaxis unnecessarily.

It is important to note that to date no screening tools for AWS have been validated in the ICU (Awissi et al., 2013). Similarly, there are no validated tools for the prediction of severe AWS in the medically ill.

To address the absence of an effective validated tool to help identify medically ill patients at risk for development of AWS prior to development of major withdrawal symptoms, we conducted a systematic literature search for the clinical risk factors for the development of moderate to severe AWS. Based on the results of this review we developed the *Prediction of Alcohol Withdrawal Severity Scale* (PAWSS). The scale's goal is to identify patients at risk for complicated alcohol withdrawal and who arguably might benefit from pharmacological intervention to prevent further morbidity and mortality. If it can be demonstrated that a patient is at risk for moderate to severe AWS, then a prophylactic treatment plan can be delivered immediately which may halt the development of complicated AWS and potentially serious complications (e.g., seizures, DT, neurodegenerative processes), as well as minimizing the detrimental effects of AWS on neurocognition.
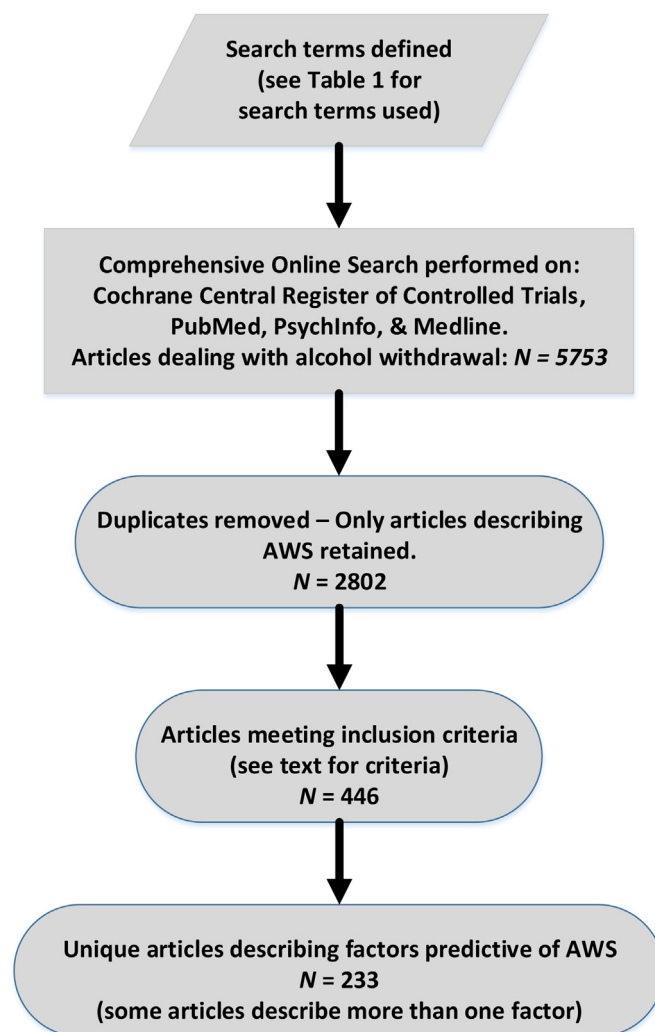
Methods

Tool design

The development of the PAWSS involved three steps. First, the authors developed a list of key words related to all forms of and predisposing factors for AWS. Using PRISMA guidelines for reporting systematic reviews (Liberati et al., 2009; Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009), we conducted a systematic literature search for clinical factors associated with the development of alcohol withdrawal syndromes (AWS). By applying the key words list, four electronic databases (i.e., Cochrane Database of Systematic Reviews, PubMed, PsychInfo, and MEDLINE) were searched for potentially relevant articles published from January 1966 to January 2011. The key terms used for all databases are listed in Table 1. The initial search was independently performed by four members of the research team using the listed databases and scrutinizing these articles' bibliographies for additional pertinent references, yielding a total of 5753 potential citations. The searches were combined, all duplicate articles were removed, and the remaining articles were reviewed to look for those exclusively dealing with AWS (based on the title and abstract), yielding a total of 2802 articles. Finally, all retrieved articles were screened to meet the following inclusion criteria: (i) manuscripts dealing with human subjects, age 18 years or older; (ii) manuscripts directly addressing descriptions of AWS or its predisposing factors, including case reports, naturalistic case descriptions and all types of clinical trial (e.g., randomized, single-blind, or open label studies); (iii) manuscripts describing characteristics of AUD; (iv) manuscripts dealing with animal data (considered only if they directly dealt with variables described in humans either corroborating or refuting human data). The resulting 446 articles were searched for factors potentially associated with increased risk for AWS, increased severity of withdrawal symptoms, and potential characteristics differentiating subjects with various forms of AWS (i.e., uncomplicated withdrawal versus complicated withdrawal, defined as hallucinosis, seizures, or DT), with a yield of 233 unique articles describing predictive factors for AWS. Please see Fig. 1 for a description of the algorithm used for the search.

Table 1
Key words used in comprehensive literature review.

Withdrawal
Alcohol withdrawal
Alcohol withdrawal seizures
Alcohol withdrawal syndrome
Delirium tremens
Prediction of alcohol withdrawal
Prediction of alcohol withdrawal seizures
Prediction of delirium tremens
Risk factors for alcohol withdrawal
Predictors of alcohol withdrawal
Predictors of alcohol withdrawal seizures
Predictors of delirium tremens
Predictors of withdrawal
Risk factors for alcohol withdrawal seizures
Risk factors for delirium tremens
Risk factors for alcohol withdrawal
Severe alcohol withdrawal syndrome
Factors predictive of severe alcohol withdrawal
Factors predictive of complicated alcohol withdrawal
Clinical predictors for alcohol withdrawal
Clinical predictors for delirium tremens
Clinical predictors for alcohol withdrawal seizures

Fig. 1. Literature search algorithm − based on PRISMA guidelines for reporting systematic reviews.

The Prediction of Alcohol Withdrawal Severity Scale (PAWSS)

The PAWSS was constructed from the 10 most relevant clinical factors, as per the systematic literature review, associated with the development of AWS. PAWSS consists of three parts: (A) The threshold criteria, whether the patient consumed alcohol during the 30 days prior to admission and/or had a positive blood alcohol level (BAL) on admission, followed by a series of 10 Yes/No questions from (B) patient interview, and (C) clinical evidence, assessing known risk factors for withdrawal and current clinical status (see Fig. 2: PAWSS Tool).

The threshold question was added because a patient who has not consumed alcohol in the 30 days preceding the encounter is postulated to be outside the "window for withdrawal" and unlikely to experience AWS, whether or not the patient has an AUD (Hall & Zador, 1997; Schuckit, 2009); at that point no further PAWSS questions are asked. If a patient does indeed endorse recent intake of alcohol (i.e., within the previous 30 days), this must be followed by 10 questions contained in the second part of PAWSS, assessing known risk factors for withdrawal and current clinical status. The PAWSS is heavily based on self-report of alcohol intake and history provided by patients, as the literature suggests that interviews by clinicians can provide the most accurate information on alcohol

Prediction of Alcohol Withdrawal Severity Scale (PAWSS)

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Part A: Threshold Criteria: (1 point either)

1. Have you consumed any amount of alcohol (i.e., been drinking) <u>within the last 30 days?</u>

   OR did the patient have a "+" BAL upon admission? _____

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

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

2. Have you <u>ever</u> experienced previous episodes of alcohol withdrawal? _____

3. Have you <u>ever</u> experienced alcohol withdrawal seizures? _____

4. Have you <u>ever</u> experienced delirium tremens or DT's? _____

5. Have you <u>ever</u> undergone of alcohol rehabilitation treatment? _____

   (i.e., in-patient or out-patient treatment programs or AA attendance)

6. Have you <u>ever</u> experienced blackouts? _____

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 <u>SCREENING TOOL</u>. The greater the number of positive findings, the higher the risk for the development of alcohol withdrawal syndromes. A score of ≥ 4 suggests HIGH RISK for moderate to severe AWS; prophylaxis and/or treatment may be indicated.

Fig. 2. PAWSS tool.

abuse and relapse, as compared to collateral information or selected laboratory data (e.g., BAL) (Cherpitel et al., 2007; DiMartini et al., 2001).

Pilot study

After the tool was constructed, a pilot study was conducted using the PAWSS as part of a quality improvement (QI) effort by the Department of Medicine to improve recognition of AWS in the general medical wards. The pilot was conducted over a 2-week period (February–March 2011) at Stanford Hospital, a tertiary care medical facility. Patients 18 years of age and older, consecutively admitted to two selected general inpatient medical units, were approached by the medicine resident conducting the Quality Improvement (QI) project for enrollment in the project regardless of the initial reason for hospitalization. The only exclusion criteria included: a patient's unwillingness to participate in the study or a patient's inability to understand and communicate in English, as PAWSS has not been translated into any other language. Upon agreement to participate in the study, PAWSS was administered by the same internal medicine resident. All patients were asked the first PAWSS "screening" question. Only those with a positive screen were asked the 10 follow-up questions in a protocoled manner.

Standard care was independently delivered to all patients by the internal medicine team (who were blinded to PAWSS scores) and PAWSS results did not influence the treatment course. Close monitoring specifically for AWS and administration of CIWA-Ar (Sullivan et al., 1989) were carried out by the primary team when deemed necessary, based on usual standards of care. Patients who experienced AWS by clinical criteria were closely clinically followed and treated with a benzodiazepine-based protocol by the primary medical team, as customary procedure.

The research team then retrospectively collected information on all patients enrolled in the study, including demographic

information, primary diagnoses, clinical history, CIWA-Ar scores, vital signs, and medication used. Every patient's chart was analyzed retrospectively for evidence of the presence or absence of AWS (according to DSM IV-TR criteria) based on patients' hospitalization histories, discharge diagnoses, vital signs, and medications used, by a group of researchers independent of the original examiner. The study was approved by the Stanford Institutional Review Board (*Protocol # 26469*).

Statistical analysis

A single rater of the scale was used for this pilot study. Age averages with standard deviations and gender percentages were calculated for demographic description of the sample. The specificity and sensitivity for each possible cut-off point for the scale (i.e., 1–10) were calculated and the cut-offs with optimal sensitivity and specificity were considered. Positive and negative predictive values for the tool, given this threshold of 4 yielding a positive screen, were also calculated.

Results

After a thorough literature search and analysis, risk factors for moderate to severe alcohol withdrawal were compiled from the literature review and distilled to 10 risk factors based on supporting evidence (see Fig. 1 – PAWSS).

(1) Previous episodes of alcohol withdrawal

The strongest predictor for the development of withdrawal syndromes is a personal or family history of alcohol withdrawal or DT (Kraemer, Mayo-Smith, & Calkins, 2003). Others have found that alcohol-dependent patients with a history of prior alcohol withdrawal or those consuming alcohol while being treated for an alcohol-related disease constitute the greatest risk for withdrawal symptoms (Benzer, 1990; Dissanaike, Halldorsson, Frezza, & Griswold, 2006; Saitz, 1998; Schuckit et al., 1995). Nearly 75% of those who experienced alcohol withdrawal seizures had a history of at least one prior hospitalization for AWS (Gross et al., 1972). In addition, studies found that the number of previous detoxifications predicted the prevalence and severity of AWS, as well as the rate of recovery from AWS (Becker, Diaz-Granados, & Weathersby, 1997; Booth & Blow, 1993; Gorelick & Wilkins, 1986; Malcolm, Roberts, Wang, Myrick, & Anton, 2000; O'Connor et al., 1991; Palmstierna, 2001; Sarff & Gold, 2010; Schuckit et al., 1995; Shaw, Waller, Latham, Dunn, & Thomson, 1998; Wojnar et al., 1999a).

Several studies found an increasing risk of severe alcohol withdrawal (e.g., seizures, DT), in both animal and human subjects with subsequent episodes of alcohol withdrawal, lending robust evidence to the "kindling hypothesis" (Becker, 1994, 1996, 1998; Becker & Hale, 1993; Hunt, 1993; McCown & Brees, 1990; Saitz, 1998). According to this model the severity of alcohol withdrawal symptoms progressively increases over years of alcohol abuse and withdrawal episodes in a stepwise fashion, resulting in lower seizure threshold and CNS excitability. Thus, limbic system hyperirritability which accompanies each alcohol withdrawal serves over time to kindle increasingly widespread subcortical structures, which may explain the progression of alcohol withdrawal symptoms from mild (e.g., tremor, irritability) to severe (e.g., seizures and DT), and may even explain the "alcoholic personality" changes observed between episodes of withdrawal.

Studies in human subjects have confirmed the presence of AWS-induced kindling, previously described in animal studies; namely, that periodic brain stimulation, particularly in the limbic system, at stimulus intensities initially too low to produce any

behavioral or EEG effects, progressively produces EEG changes, motor automatisms, and eventually convulsions (Ballenger & Post, 1978). Available data suggest that the severity of alcohol withdrawal symptoms progressively increases over years of alcohol abuse in a stepwise fashion and that the limbic system hyperirritability which accompanies each episode of alcohol withdrawal serves over time to kindle increasingly widespread subcortical structures.

A study assessing the predictive potential of a plurality of factors associated with the risk of withdrawal demonstrated that the number of preceding withdrawal episodes, in combination with other parameters (e.g., BAL on admission, nicotine abuse) was a good predictor of those at risk to develop AWS (Hillemacher et al., 2012). Similarly, a study among alcohol-dependent subjects demonstrated that those experiencing severe AWS had a history of more withdrawal episodes (28.2 ± 33.74 versus 15.9 ± 26.84) (Schuckit et al., 1995).

The notion that repeated withdrawal experience progressively intensifies withdrawal symptoms is also supported by animal models. For example, animals chronically exposed to alcohol were shown to exhibit enhanced withdrawal-related anxiety when submitted to repeated withdrawal experiences (Breese, Overstreet, & Knapp, 2005; Overstreet, Knapp, & Breese, 2004, 2005; Zhang, Morse, Koob, & Schulteis, 2007). Indeed, multiple animal models support the notion that repeated ethanol withdrawal experiences increase the severity and duration of subsequent withdrawal seizures (Becker, Diaz-Granados, & Weathersby, 1997; Becker & Hale, 1993). Furthermore, rodent experiments have demonstrated that repeated ethanol withdrawal experiences do not result in a global non-specific lowering of threshold to experience AWS, but rather, selective changes in CNS mechanisms associated with neural excitability may underlie potentiated withdrawal responses (Becker, Veatch, & Diaz-Granados, 1998).

In addition, in accordance with the central role of kindling in triggering alcohol withdrawal seizures, animal studies confirm that multiple alcohol withdrawal episodes in rats facilitate the development of inferior collicular cortex seizure activity seen in severe AWS (Gonzalez, Veatch, Ticku, & Becker, 2001; McCown & Breese, 1990, 1993). This was confirmed in a series of experiments in mice where results indicated a positive relationship between the number of previously experienced ethanol withdrawals and the severity and duration of a subsequent withdrawal episode (Carrington, Ellinwood, & Krishnan, 1984). Further, the researchers found that the intensity of withdrawal seizures progressively increased over repeated cycles of intoxication/withdrawal (Becker, Diaz-Granados, & Weathersby, 1997; Ulrichsen et al., 1998).

Animal models suggest that severe AWS (i.e., seizures) were significantly more severe in mice with multiple withdrawal experience in comparison to animals that experienced only a single withdrawal episode, even when the total amount of ethanol exposure was equated among groups, and suggest selective up-regulation of adenosine receptors during alcohol withdrawal episodes (Jarvis & Becker, 1998).

(2) Previous alcohol withdrawal seizures

Studies have found that a previous history of alcohol withdrawal-related seizures is one of the most significant risk factors for the development of severe AWS (i.e., seizures, DT) (Alcohol withdrawal syndrome: how to predict, prevent, diagnose and treat it, 2007; Avdaloff & Mauersberger, 1981; Essardas Daryanani et al., 1994; Monte et al., 2009; Morton, Laird, Crane, Partovi, & Frye, 1994; Rathlev, Ulrich, Fish, & D'Onofrio, 2000; Shaw et al., 1998; Victor & Brausch, 1967). In fact, a study found that a previous history of "withdrawal fits" more than doubled the

risk of severe AWS and increased the risk of complications (Gorelick & Wilkins, 1986).

Yet, while most studies draw a direct link between chronic alcohol use/dependence and alcohol cessation (presumably mediated via effects on both gamma-aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA) receptors) (Bartolomei, Suchet, Barrie, & Gastaut, 1997; Bråthen, 2003; Chan, 1985; Gheorghiev, De Montleau, & Defuentes, 2011; Hattemer, Knake, Oertel, Hamer, & Rosenow, 2008; Hillbom, Pieninkeroinen, & Leone, 2003; Hughes, 2009; Leach, Mohanraj, & Borland, 2012; Mayo-Smith & Bernard, 1995; Morris & Victor, 1987; Rathlev, Ulrich, Delanty, & D'Onofrio, 2006; Rogawski, 2005; Sand et al., 2010), others have suggested that there may be a significant contribution from other factors associated with alcohol abuse and withdrawal (e.g., head injury, cerebral infarcts, cerebral atrophy, sleep deprivation) (Avdaloff & Mauersberger, 1981; Bartolomei et al., 1997; Chan, 1985; Courville & Myers, 1954; Earnest et al., 1988; Earnest & Yarnell, 1976; Feuerlein, 1977; Geibprasert, Gallucci, & Krings, 2010; Giove & Gastaut, 1965; Götze, Kühne, Hansen, & Knipp, 1978; Gross & Hastey, 1975; Hund, 2003; Johnson, Burdick, & Smith, 1970; Ladurner & Griebnitz, 1986; Neundörfer et al., 1984; Niedermeyer, Freund, & Krumholz, 1981; Sullivan, Marsh, Mathalon, Lim, & Pfefferbaum, 1996; Victor & Laureno, 1978). A classic article on AWS described that "two fifths of patients experiencing 'rum fits' will progress to delirium tremens; one fourth of these patients awaken from seizure with delirium, but two fifths of the patients have a lucid interval of half a day to five days before delirium becomes manifest" (Victor & Adams, 1953).

An intriguing hypothesis proposed that repeated alcohol withdrawal seizures may render the brain more excitable, leading to an epileptogenic state reminiscent of the 'kindling' model described above. The long-term changes in neuronal excitability associated with AWS lead to a progression of alcohol withdrawal symptoms from tremor to seizures and delirium tremens (Ballenger & Post, 1978). This was confirmed in humans by comparing alcohol withdrawal seizures against seizures from non-alcoholic etiologies (Bartolomei et al., 1997). Similarly, a retrospective study among 1695 patients with AUD revealed that a prior history of a withdrawal seizure was a significant predictor of severe AWS, particularly future withdrawal seizures ($p < 0.05$) (Morton et al., 1994).

A retrospective study among alcohol-dependent males found that a past history of alcohol withdrawal seizures was a significant predictor of future episodes of DT (Cushman, 1987). Another study found a previous history of alcohol withdrawal seizures was the best predictor of subsequent withdrawal seizure susceptibility (Brown et al., 1988). Similarly, others have demonstrated a significant correlation between previous alcohol withdrawal seizures and the subsequent development of alcohol withdrawal delirium (Palmstierna, 2001). Likewise, a case-control study showed that patients suffering from DT were more likely than controls to report a prior withdrawal episode complicated by DT or alcohol withdrawal seizures (Fiellin, O'Connor, Holmboe, & Horwitz, 2002).

A prospective study of alcohol-dependent patients found subjects with a past history of alcohol withdrawal seizures were more likely to experience withdrawal seizures during the index hospitalization ($p < 0.001$) (Essardas Daryanani et al., 1994). In another study, the likelihood of withdrawal seizures and the number of alcohol withdrawal seizures was significantly higher among those patients with a past history of alcohol withdrawal seizures ($p = 0.002$) (Eyer et al., 2011). In fact, studies have found that along with increased signs of autonomic activity, a past history of seizures among alcohol-dependent subjects was one of the best predictors of progression to DT (Monte et al., 2009; Monte Secades et al., 2008).

(3) History of DT

The theory of kindling described above suggests that the neuronal excitability associated with repeated episodes of AWS leads to a progression of symptoms from tremor to seizures and it may contribute to the development of delirium tremens; thus, the greater the number of prior episodes of DT the greater the risk of DT during an episode of alcohol withdrawal (Ballenger & Post, 1978).

An early study found that a history of DT was a strong predictor of future AWS, including DT (Ferguson et al., 1996). In a retrospective cohort study, a "self-reported history of DT" was found to be an independent correlate of severe withdrawal (Kraemer et al., 2003). Some studies have suggested that the most significant risk factors for severe AWS include: chronic heavy drinking, a history of generalized seizures, and a history of delirium tremens (Alcohol withdrawal syndrome: how to predict, prevent, diagnose and treat it, 2007; Lee et al., 2005; Monte et al., 2009).

Several studies have found that a previous history of DT was a significant predictor of future episodes of DT (Cushman, 1987; Lee et al., 2005; Wright, Myrick, Henderson, Peters, & Malcolm, 2006). In addition, a study found that the duration of delirium tremens was positively correlated to the number of previous delirium tremens (Stendig-Lindberg & Rudy, 1980). Finally, a prospective study of alcohol-dependent patients demonstrated that those who reported previous episodes of delirium tremens had significantly larger cortical atrophy on CT scans (Essardas Daryanani et al., 1994).

(4) History of alcohol rehabilitation treatment

Patients with a history of multiple detoxification episodes are more likely to experience seizures and severe withdrawal symptoms (Yost, 1996). Preclinical and clinical evidence has demonstrated that a history of multiple detoxification experiences can result in increased sensitivity to the withdrawal syndrome via kindling (Becker, 1994, 1996, 1998, 2000; Becker, Diaz-Granados, & Hale, 1997; Becker & Hale, 1993). Clinical studies have suggested that a history of multiple detoxifications increases a person's susceptibility to more severe and medically complicated withdrawals in the future (Booth & Blow, 1993). Data suggest that the severity of alcohol withdrawal symptoms progressively increases over years of alcohol abuse and that repeated detoxifications augment the likelihood of alcohol withdrawal seizures (Duka et al., 2004).

Several large-scale human studies have demonstrated a significant correlation between an increased number of prior detoxifications and the incidence of withdrawal seizures on the index admission (Booth & Blow, 1993; Brown et al., 1988; Lechtenberg & Worner, 1990). Another study found significant associations between seizure prevalence and both recurrent alcohol detoxification and average daily ethanol consumption (Lechtenberg & Worner, 1992).

A study found that subjects who had received alcohol rehabilitation treatment (inpatient and outpatient) were significantly more likely to have experienced AWS and DT than subjects with no prior history of treatment (Raimo, Daeppen, Smith, Danko, & Schuckit, 1999). Another study found that prior participation in at least two alcohol treatment programs was an independent correlate of severe withdrawal (Kraemer et al., 2003), while others have identified a history of prior detoxification as a risk factor for severe AWS (Saitz, 1998).

In a study of 300 alcohol-dependent subjects there was a significant correlation between the number of prior inpatient alcohol detoxifications and the prevalence of alcohol withdrawal seizures (Lechtenberg & Worner, 1990). Finally, a study of alcoholic subjects, with and without a history of withdrawal seizures, demonstrated that alcoholics with greater than five previous medical

detoxifications may be at a higher risk for withdrawal seizures due to the accumulated kindling effect of repeated alcohol withdrawals (Brown et al., 1988). Several large-scale human studies have demonstrated a significant correlation between an increased number of prior detoxifications and the incidence of withdrawal seizures on the index admission (Booth & Blow, 1993; Brown et al., 1988; Lechtenberg & Worner, 1990). Another study found significant associations between seizure prevalence and both recurrent alcohol detoxification and average daily ethanol consumption (Lechtenberg & Worner, 1992).

(5) Previous episodes of blackouts

Blackouts are transient episodes of amnesia (usually retrograde), without loss of consciousness, that accompany various degrees of alcohol intoxication (Carpenter, 1962; Goodwin, 1971; Lisman, 1974). It is suggested that a considerable degree of alcohol tolerance must be present so that a sufficient amount of alcohol may be ingested to trigger such an episode (Tamerin, Weiner, Poppen, Steinglass, & Mendelson, 1971). Indeed, a high BAL is seen as a necessary component for the occurrence of alcoholic blackouts (Cutting, 1982; Goodwin & Hill, 1973; Lisman, 1974). Studies on the occurrence of alcoholic blackouts characterized blackouts as an accurate indication of advanced intoxication and the severity of alcoholism (Goodwin, Crane, & Guze, 1969a, b; Goodwin & Hill, 1973). In their sample, blackouts were a relatively late manifestation of alcoholism, preceded by benders (i.e., binge drinking, defined as continuous intoxication for ≥2 working days), tremulousness, and, often, severe social repercussions from drinking. In this sample 50% of subjects experienced DT before or during the same year as their first blackout. According to the authors, the more severe the alcoholism, the more likely blackouts are to occur.

The blood alcohol levels required to reach this state indicate significant tolerance (Sweeney, 1989). Studies indicate that individuals with a history of alcoholic blackouts usually show a higher average quantity of alcohol intake compared to alcohol-dependent patients without blackouts (Zucker, Austin, & Branchey, 1985). The same study found that blackouts predicted the development of other alcohol withdrawal-related symptoms such as tremors and hallucinations. Similarly, the assessment of alcohol consumption among an age-stratified, random sample of men revealed that, as expected, the frequency of blackouts increased with the amount of alcohol consumed (Mützell, Tibblin, & Bergman, 1987).

More recent literature continues to support this association, as the British 2010 National Clinical Guidelines state that blackouts are suggestive of physical dependence (NHS, 2010). Others have demonstrated that the frequency of intoxicating drinking was significantly associated with the frequency of blackouts (Poikolainen, 1982). Multiple studies have found that the severity of alcohol dependence predicts the severity of withdrawal symptoms (Chang & Steinberg, 2001; Shaw et al., 1998).

A study of young university students found that those with a history of blackouts began drinking at an earlier age ($p < 0.005$), consumed alcohol more frequently ($p < 0.005$) and in a greater quantity ($p < 0.001$) than those without a history of blackouts (Anthenelli, Klein, Tsuang, Smith, & Schuckit, 1994). In other words, blackouts are associated with the quantity and frequency of drinking.

Finally, in a large study among drinking men, multiple regression analysis revealed that the frequency of blackouts was significantly associated with age and frequency of drinking to intoxication (an almost linear increase with the frequency of intoxication) (Poikolainen, 1982).

(6) Concomitant use of CNS-depressant agents, such as benzodiazepine or barbiturates

Studies examining correlates of alcohol withdrawal identified recent exposure to and concomitant use of barbiturates and benzodiazepines to be associated with severe AWS (Kraemer et al., 2003; Schuckit et al., 1995; Sellers, 1988; Wadstein & Skude, 1978; Wetterling, Kanitz, Veltrup, & Driessen, 1994; Wojnar et al., 1999b; Wojtecki, Marron, Allison, Kaul, & Tyndall, 2004). One study found that the concomitant use of depressant psychoactive substances was a significant factor associated with the development of alcohol withdrawal-related seizures (Morton et al., 1994).

A study among alcohol-dependent subjects demonstrated that those experiencing severe AWS had a history of more non-medicinal use of sedative-hypnotics (56.4% versus 32.9%; $p < 0.001$) (Schuckit et al., 1995). This figure is consistent with subsequent studies which have found that 53% of benzodiazepine-dependent subjects had a lifetime prevalence of alcohol dependence (Busto, Romach, & Sellers, 1996).

Furthermore, increased severity and duration of withdrawal symptoms were reported in patients who concomitantly abused benzodiazepines or barbiturates compared to those who did not (Morton et al., 1994; Rathlev et al., 2006; Wojnar et al., 1999b). Consider the fact that nearly 80–97% of benzodiazepine-dependent patients experience withdrawal symptoms upon cessation or decreased dosing (Busto et al., 1996; Busto & Sellers, 1991; Busto, Sellers, Naranjo, Cappell, Sanchez-Craig, Sykora, 1986). This may then aggravate the symptoms of AWS. Similarly, the symptoms of benzodiazepine withdrawal may be indistinguishable from those of alcohol withdrawal (Busto & Sellers, 1991; Busto, Sellers, Naranjo, Cappell, Sanchez-Craig, & Simpkins, 1986). It is postulated that withdrawal states from benzodiazepines or barbiturates may be related to, or intensify the severity of, the alcohol withdrawal episodes. In these cases, the risk for developing severe withdrawal symptoms is substantially higher.

Similar problems may be expected with concomitant abuse of alcohol and barbiturates. In fact, the proportion of barbiturate-dependent patients who experience withdrawal symptoms is about 100%, while withdrawal seizures occur in 78% (Fraser, Isbell, Eisenman, Wikler, & Pescor, 1954). As in the case of alcohol, the symptoms of severe barbiturate withdrawal are similar to those of severe AWS, including grand mal seizures and delirium (Fraser, Wikler, Essig, & Isbell, 1958). Clinicians also need to consider pharmacokinetic and dynamic variables when it comes to alcohol – sedative/hypnotic interactions. Chronic alcohol administration induces enzymatic metabolism, increasing drug clearance (e.g., benzodiazepines, barbiturates), thus contributing to lesser therapeutic effect and potentially precipitated withdrawal syndromes (Sellers, 1988; Sellers & Busto, 1982). There is also evidence suggesting that chronic ethanol ingestion might not only decrease blood levels of benzodiazepines, but also decrease central nervous system (CNS) sensitivity (Sellers & Kalant, 1978).

(7) Concomitant use of other illicit substances

A study revealed that a substantial number of patients who experienced severe withdrawal self-reported abusing other substances, and in larger variety (e.g., amphetamines, cannabinoids, cocaine, opiates, and sedatives) (Schuckit et al., 1995). Another study found that patients with a history of psychotropic drug use were 2.25 times more likely to have a seizure than those without such a history (Newsom, 1979). Others have identified the use of other substances, in addition to alcohol, as a risk factor for DT and seizures (Saitz, 1998). A study among alcohol-dependent subjects demonstrated that those experiencing severe AWS had a history of

other concomitant substance dependence, other than alcohol (48.8% versus 31.5%; $p < 0.001$) (Schuckit et al., 1995). Similarly, a study of patients admitted for the management of AWS revealed that having a positive urine drug screen for a non-alcohol drug was associated with a greater number of admissions for AWS ($p = 0.0002$) (Larson et al., 2012). Thus, multiple studies and surveys, including the National Comorbidity Survey and the National Survey on Drug Use and Health, found that a substantial number of individuals with an alcohol-use disorder suffer a comorbid substance-use disorder (Kessler et al., 1997; Saitz et al., 1995; SAMHSA, 2009, 2012; Tsuang, Shapiro, Smith, & Schuckit, 1994).

Of note, others have demonstrated that nicotine dependence is associated with alcohol consumption and that the number of cigarettes smoked (reflecting the intake of toxic nicotine) was positively associated with the individual risk of alcohol withdrawal seizures (Hillemacher et al., 2012). Both smoking and high nicotine dependence have been associated with use of alcohol, among other substances, and may have a central facilitating role in the use of alcohol and illegal drugs, as well as exacerbating the withdrawal symptoms of other substances, including alcohol (Martinez-Ortega, Jurado, Martinez-González, & Gurpegui, 2006; Romberger & Grant, 2004; Stewart & Brown, 1995).

(8) Recent episode of alcohol intoxication

This item allows clinicians to determine whether the patient recently consumed alcohol to the extent that the patient experienced the effects of alcohol in the days preceding their PAWSS assessment. Some have reported that patients with higher daily levels of alcohol intake, resulting in higher blood alcohol concentrations, are at risk of more severe AWS, including seizures and DT (Saitz, 1998). A study found that in subjects with a median daily alcohol consumption of >100 g of alcohol (standard drink = 12 g of alcohol), the incidence of withdrawal seizures and delirium was 17% before preventive measures could be initiated (Foy et al., 1997). Another found a significant correlation ($r = 0.55$; $p < 0.01$) between the severity of withdrawal and the total alcohol intake in the days immediately prior to admission (Pristach, Smith, & Whitney, 1983).

Previous studies have found that consumption of greater amounts of alcohol and more severe alcohol dependence predict more severe AWS (Schuckit et al., 1995). The evidence suggests that signs of autonomic hyperactivity associated with complicated alcohol withdrawal typically appear 24–96 h post cessation of [heavy] alcohol use (Mayo-Smith et al., 2004). Others have found a positive correlation between the severity and duration of DT symptoms and the daily amount of alcohol consumed during the last drinking episode (Gorelick & Wilkins, 1986; Wojnar et al., 1999b).

A study of 500 alcohol-dependent subjects found a direct correlation between average daily alcohol consumption and the prevalence of alcohol-related seizures (Lechtenberg & Worner, 1992). Similarly, a retrospective study of AUD patients found a significant relationship between a history of daily heavy alcohol use and future episodes of DT (Cushman, 1987). A study among alcohol-dependent patients demonstrated that with an increasing daily dose of alcohol use there is an increased risk of severe AWS, particularly seizures. In this sample, the adjusted odds ratios rose from 3-fold among subjects ingesting 51–100 g of ethanol per day (95% confidence limits, 1.3 and 6.3), to 8-fold at ingestions of 101–200 g per day (95% CI, 3.3 and 18.7), and to almost 20-fold for those ingesting 201–300 g per day (95% CI, 6.1 and 6.2) (Ng, Hauser, Brust, & Susser, 1988).

A large study of 1648 alcohol-dependent subjects suggested that the maximum number of drinks per day and the total number of withdrawal episodes were the most powerful differences between those with severe withdrawals (DT and alcohol withdrawal seizures) and those alcohol-dependent patients not experiencing severe AWS (Schuckit et al., 1995). Overall, a history of chronic heavy drinking, generalized seizures, and DT have been found to correlate with the development of severe AWS (Alcohol withdrawal syndrome: how to predict, prevent, diagnose and treat it, 2007).

(9) Blood alcohol level (BAL) on admission

The quantity and frequency of alcohol intake is positively associated with the severity of alcohol withdrawal symptoms, as is the experience of alcohol withdrawal symptoms at blood alcohol concentrations greater than 1 g/L (Palmstierna, 2001; Schuckit et al., 1995; Shaw, Kolesar, Sellers, Kaplan, & Sandor, 1981; Wojnar et al., 1999b). Some have described how the total consumption of alcohol predicts the development of severe AWS, particularly withdrawal seizures (Lechtenberg & Worner, 1992). In one particular study, elevated heart rate and signs of autonomic overactivity coupled with an alcohol concentration of more than 1 g/L of body fluid was predictive of the development of DT (Palmstierna, 2001).

The BAL at the time of admission to the hospital has been correlated with severity of AWS. One retrospective cohort study of 185 subjects admitted for alcohol detoxification demonstrated a significant correlation between blood alcohol level on admission and severity of alcohol withdrawal course ($p < 0.0001$) (Vinson & Menezes, 1991). Another large study ($n = 1648$) of alcohol-dependent subjects found a relationship between the number of drinks in any 24-h period and severity of withdrawal symptoms (Schuckit et al., 1995). A large retrospective study among motor vehicle trauma victims revealed that 51% of trauma patients with an admission BAL >200 experienced complications during their hospital course, among which was higher rates of AWS (Kapur, Rajamanickam, & Fleming, 2010). In fact, the authors found a strong dose–response effect between BAL and risk of alcohol withdrawal: patients with a BAL >200 mg/dL had a 30-fold risk (OR = 30.96, 19.5–49.2) of withdrawal and those with a BAL < 100 mg/dL had a 12-fold risk (OR = 12.02, 7.0–20.7) compared to persons with a negative BAL (Kapur et al., 2010).

Others have demonstrated that among the factors associated with the risk to developing AWS, admission BAL, usually in combination with other parameters (e.g., number of previous AWS episodes, nicotine abuse), was one of the best predictors (Hillemacher et al., 2012).

(10) Evidence of increased autonomic activity

Signs of increased autonomic activity on admission have been associated with development of alcohol withdrawal seizures and increased severity of alcohol withdrawal. It has been postulated that increased noradrenergic activity (along with other central and peripheral regulating mechanisms) is likely the factor associated with cardiovascular changes in AWS (Kähkönen, Zvartau, Lipsanen, & Bondarenko, 2011; King, Errico, Parsons, & Lovallo, 1991; Potter, Bannan, Saunders, Ingram, & Beevers, 1983). In alcohol-dependent subjects, a significant decrease in excretion of VMA and a concomitant increase in MHPG excretion occurred upon cessation of alcohol intake (Ogata, Mendelson, Mello, & Majchrowicz, 1971). These changes suggest that chronic ethanol ingestion is associated with both stimulation of adrenergic activity and alteration in pathways of catecholamine catabolism. Plasma noradrenaline and platelet alpha-2 adrenoceptor density were correlated with the withdrawal score among hospitalized patients undergoing alcohol withdrawal (Smith, Brent, Henry, & Foy, 1990). Similarly, the destruction of noradrenergic systems in the brain by administration

of 6-hydroxydopamine prior to chronic ethanol treatment prevented the development of tolerance to ethanol (Tabakoff, Ritzmann, & Hoffman, 1977).

A study of 303 alcohol-dependent subjects examining the factors associated with development of DT among patients admitted with AWS found that systolic blood pressure >150 mm Hg [OR 1.9 [CI 95% 1.1—3.8, $p = 0.03$] and axillary temperature > 38 °C [OR 1.9 (CI 95% 1.05—3.5), $p = 0.01$] were both independently associated with progression to DT (Monte et al., 2009). Another study highlighted tachycardia (HR > 120 beats per minute [bpm]) and other signs of autonomic overactivity (e.g., sweating, tremor, agitation, nausea) accompanied by an alcohol concentration of more than 1 g/ L of body fluid as significant correlates to the development of DT (Palmstierna, 2001). Others have demonstrated that the 24-h mean heart rate was higher in the alcoholic men (97.4 beats/minute, 95% confidence interval (CI) 91.2—103.6) than in the controls (69.6 beats/minute, 95% CI 65.4—73.8, $p < 0.001$) (Denison, Jern, Jagenburg, Wendestam, & Wallerstedt, 1994).

Others demonstrated that an elevated heart rate ≥100 bpm on admission was predictive of development of seizures and DT during the index admission (Lee et al., 2005; Morton et al., 1994). Similarly, elevated blood pressure on admission has been shown to be predictive of consecutive development of DT (Fiellin et al., 2002). In addition, a study of 436 alcohol-dependent men found that those progressing to develop DT had greater elevations in temperature, heart rate, and blood pressure, as well as more convulsions than minor withdrawal cases (Monte Secades et al., 2008). Others have demonstrated how AWS patients hypertensive at the first admission had significantly longer duration of delirium during the course of their hospitalization (Burapakajornpong, Maneeton, & Srisurapanont, 2011).

While these studies demonstrate an association between elevated autonomic activity and increased severity of AWS among patients admitted for alcohol consumption, it can be extrapolated that similar measures of increased autonomic activity can predict progression to severe AWS in patients admitted for other indications (e.g., general medicine and surgery). Finally, several studies observed a significantly higher risk of severe alcohol withdrawal in patients with more than one of the ten factors listed above, as included in PAWSS (Abraham, Shoemaker, & McCartney, 1985; Burapakajornpong et al., 2011; Ferguson et al., 1996; Kraemer et al., 2003; Lee et al., 2005). For example, among 147 subjects with alcohol dependence, multiple logistic regression analysis demonstrated that a previous history of DT (odds ratio (OR) 3.990; 95% CI 1.631, 9.759) and high pulse rate above 100 bpm (OR 4.158; 95% CI 2.032, 8.511) were significant predictors for developing DT. Furthermore, if one predictor was present, DT developed in 45.6%, but if two predictors were present, DT developed in all cases (100%) (Lee et al., 2005).

PAWSS pilot study outcomes

Over the study period, 69 patients consecutively admitted to the selected general medical wards were approached for inclusion into this pilot study. Of those, only one patient declined to participate. The remaining 68 patients consented for participation and were asked the PAWSS screening question regarding the use of alcohol within 30 days of index hospital admission. Tables 2 and 3 provide details of the patient's demographic data and the sample's primary admission diagnosis, respectively. Fifty-one subjects screened negative on PAWSS. The remaining 17 patients who endorsed using alcohol within the last 30 days were further assessed with Parts B and C of PAWSS (see Fig. 3 for study flow diagram). Out of these 17 patients, 7 had a PAWSS score of 0; 6 had a PAWSS score of 1—3; the remaining 4 had a PAWSS score of 4 or

greater (i.e., 5, 6, 8, 9). Cut-offs of 3, 4, or 5 are valid given these plot data; four (4) was chosen as the threshold for consideration of a positive PAWSS screen, being in the middle of the transition range (see Table 4). Fig. 4 shows the ROC analysis suggesting optimal PAWSS score cut-off. None of the 13 patients with a negative PAWSS score (as defined by PAWSS of 3 or below) developed complicated AWS, while all 4 patients who had a PAWSS score of 4 or above developed complicated alcohol withdrawal as defined by their clinical presentation and/or CIWA-Ar scores. A PAWSS score of 4 or above accurately predicted a patient at high risk for the development of moderate (i.e., hallucinosis) to severe (i.e., seizures, DT) AWS. All patients with a PAWSS ≥4 required treatment with benzodiazepine agents to manage withdrawal symptoms.

In addition, none of the 51 patients who denied alcohol use during the 30 days prior to index admission were diagnosed with alcohol withdrawal by their primary team physicians during the hospital stay. A retrospective review of their hospital charts revealed no evidence of AWS during the index hospitalization.

Of note, a total of 6% of patients in this sample developed complicated AWS (4 out of 68 patients). This agrees closely with the reported incidence in previous studies (Benzer, 1990; Maldonado et al., 2010; Saitz & O'Malley, 1997; Schuckit et al., 1995). Patients who developed complicated alcohol withdrawal, as predicted by PAWSS, tended to be younger and were more likely to be male, but these differences were not statistically significant. This pilot data translated into 100% sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the PAWSS using 4 as the threshold for a positive PAWSS score in identifying those patients who will develop complicated AWS. Please see Table 5 for details.

Table 2
PAWSS study results — demographic data.

Patient groups (n)	Age, average (SD)	% male
Negative screen (51)	63.1 (19.3)	31.4%
PAWSS 0—3 (13)	65.3 (18.6)	38.5%
PAWSS ≥4 (4)	50 (11.1)	50%

Table 3
Sample's primary admission diagnosis.

Primary diagnoses	N	%
Abdominal		
Pain (e.g., cirrhosis, pancreatitis, gastroenteritis, cholangitis, mesenteric ischemia, Crohn's/ulcerative colitis, *C. difficile* colitis)	14	20.6
Gastrointestinal bleed	7	10.3
Respiratory		
Pneumonia	12	17.6
Other (pulmonary embolism, COPD exacerbation, pleural effusion, amyotrophic lateral sclerosis)	4	5.9
Cardiovascular (CHF, hypotension, syncope)	4	5.9
Infectious, other than abdominal and respiratory (bacteremia, sepsis, *C. diff* colitis, cellulitis, graft infection)	9	13.2
Hematologic (anemia, neutropenia, DVT)	3	4.4
Neuropsychiatric		
Altered mental status/delirium	3	4.4
Seizure	1	1.5
Alcohol withdrawal	1	1.5
Head trauma	1	1.5
Musculoskeletal (hip pain/fracture, rhabdomyolysis)	3	4.4
Other (anaphylaxis, dehydration, hematuria, hyponatremia, neck mass, rectal prolapse)	6	8.8
Total	68	100

COPD = chronic obstructive pulmonary disease; CHF = congestive heart failure; DVT = deep venous thrombosis.
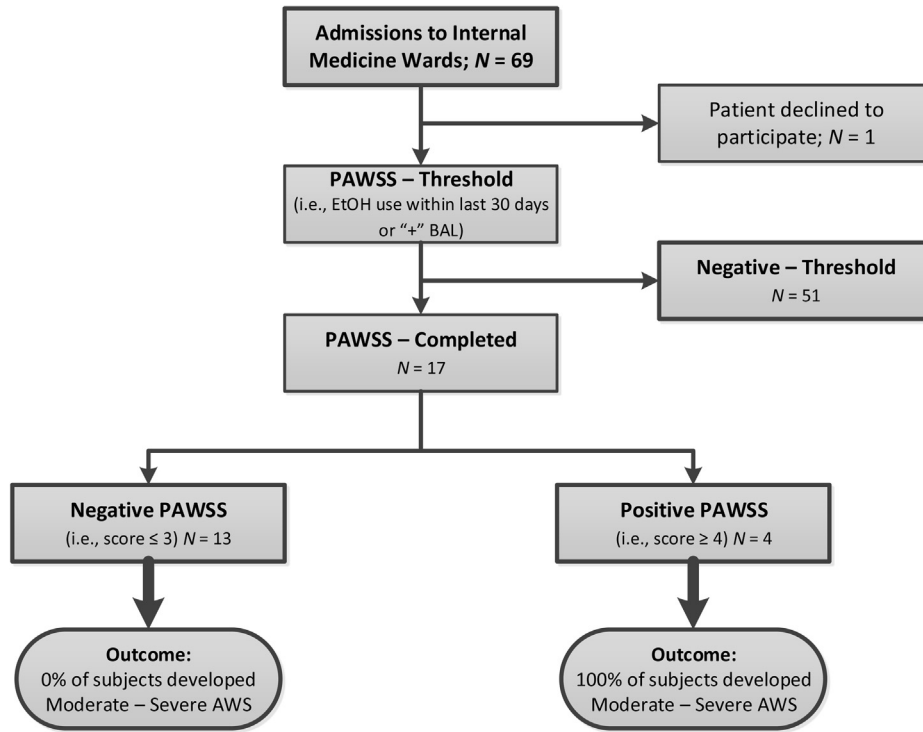
Fig. 3. PAWSS pilot study – flow chart.

Adverse events

There were no adverse events reported during the course of the study.

Discussion

Based on our review of the literature of factors associated with alcohol withdrawal severity, we have developed a new tool, PAWSS, designed to identify patients at risk for moderate to severe AWS. The pilot study demonstrated 100% sensitivity, specificity, PPV, and NPV of the PAWSS' ability to predict complicated alcohol withdrawal in this inpatient medical population. While the tool takes less than a minute to be administered and minimally adds to the overall cost of an inpatient stay, it has the potential to accurately identify those patients who are at high risk to develop complicated AWS.

If we can accurately predict and manage patients at high risk before they develop symptoms of AWS, we could potentially improve their clinical outcomes, diminish suffering, shorten hospitalizations, and decrease associated care costs. Moreover, by preventing these patients from experiencing AWS with prophylactic treatments, we can potentially stop the cycle of ever worsening their future episodes of AWS and protect their current cognitive functioning. While there are known risk factors for AWS, such as the ones used in the development of the PAWSS, until now there has been no standardized way to apply them to predict someone at risk. No simple measure, such as BAL, has been validated on its own to correctly predict those at risk. Thus, patients'

Table 4
PAWSS study results – calculation of cut-off.

Threshold (PAWSS score)	Sensitivity (%)	Specificity (%)
1	100.0	90.6
2	100.0	98.4
3	100.0	100.0
4	100.0	100.0
5	100.0	100.0
6	75.0	100.0
7	50.0	100.0
8	50.0	100.0
9	25.0	100.0
10	0.0	100.0

Cut-offs of 3, 4, or 5 are valid given these plot data. Four (4) was chosen as being in the middle of the transition range. For reference see Fig. 4.
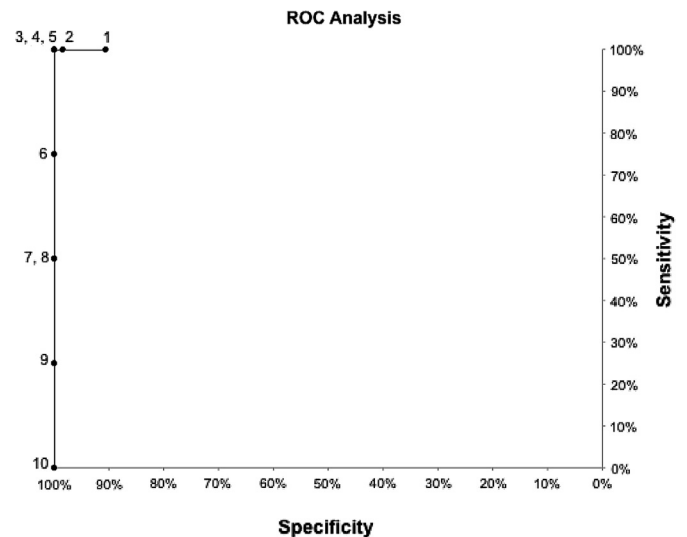

Fig. 4. ROC-analysis of PAWSS optimal cut-off score cut-offs of 3, 4, or 5 are valid given these plot data. Four (4) was chosen as being in the middle of the transition range. For reference see Table 4.

Table 5
Calculating specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV).

	AWS "+" (n)	AWS "−" (n)	Total (n)
PAWSS "+"	True positives (TP) 4	False positives (FP) 0	All PAWSS "+" 4
PAWSS "−"	False negatives (FN) 0	True negatives (TN) 64	All PAWSS "−" 64
Total	Patients with AWS (AWS "+") 4	Patients with no AWS (AWS "−") 64	Total patients 68

Sensitivity = TP/"AWS +" = 4/4 = 100%.
Specificity = TN/"AWS −" = 64/64 = 100%.
PPV = TP/"PAWSS +" = 4/4 = 100%.
NPV = TN/"PAWSS −" = 64/64 = 100%.

estimate of risk and subsequent quality of treatment is left to individual providers' judgment and preferences. PAWSS has the potential to fill this gap and could be instrumental in improving the medical and neurocognitive outcomes of the inpatients that are at high risk for AWS as well as decreasing the costs of medical admissions. PAWSS can be a simple, efficient, and very cost-effective screening tool used on any patients presenting to the emergency department or admitted to the hospital.

There are several limitations of this pilot study. First, patients reporting no alcohol intake during the last 30 days were not asked the full battery of PAWSS questions and were assumed to be of low risk. It is possible that some of these patients concealed their alcohol use and were thus inaccurately excluded from the full PAWSS administration and potentially their risk for AWS was inaccurately predicted. However, at this stage PAWSS administration did not influence or change how patients were monitored or cared for by their primary teams. Moreover, a careful retrospective chart analysis of the patients involved found no evidence of AWS during the index admission. If patients in this group did indeed have missed symptoms of AWS, these were likely to have been mild and not necessitating pharmacological treatment. In addition, the study is limited by the fact that a single rater was utilized. This was due to the fact that this was a pilot feasibility study. In future studies to replicate results on a larger sample, we plan to utilize multiple raters to investigate the tool's inter-rater reliability. Finally, the patient sample size was small and thus the results cannot be easily generalized at this time.

To further validate the tool we are in the process of conducting a larger trial with adequate power, using multiple raters to determine inter-rater reliability. It is possible that not all items on the current version of the PAWSS need to be present to maintain excellent psychometric characteristics, and factor analysis with a larger sample should allow for a determination of factors driving predictive value.

We propose that, while adding minimal time and cost to the overall care, PAWSS will be a useful tool for the prompt and accurate identification of patients at risk for complicated AWS before they develop such symptoms, allowing these patients to receive effective prophylaxis, instead of waiting for the development of AWS. This will help preserve these patients' neuropsychiatric functioning, stop further cascade of deterioration and increased risk, improve morbidity and mortality, and reduce overall costs of care.

Acknowledgments

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