

Severe alcohol withdrawal syndrome: review of the literature

Benson, George; Roberts, Nicola; McCallum, Jacqueline; McPherson, Andrew

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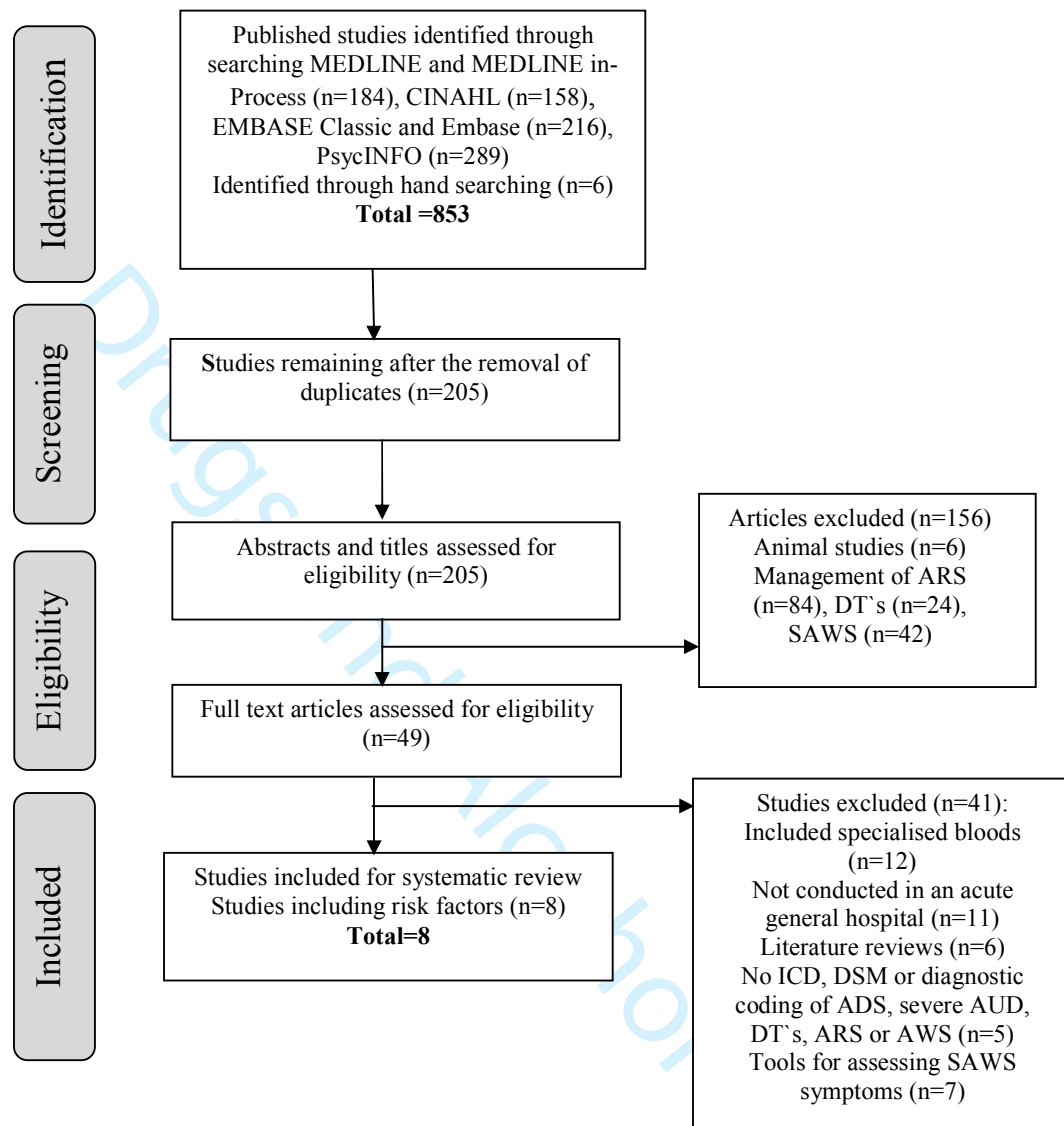


FIGURE 1. Results of searches and screening processes used to identify appropriate papers.

PRISMA Flow Diagram (Adapted from Moher et al., 2009).

TABLE 1. Literature search strategy

Search terms	Hospital, general, acute, alcoholic, alcoholism, dependence, alcohol addiction, problem drinker, harmful drinker, alcohol misuser, alcohol abuser. (Population) History, assessment, medical history, drinking history, risk assessment, CIWA-Ar, prediction, prediction tools, identification, treatment. (Intervention) Risk factors, blood, biomarkers, age, blood pressure, pulse, comorbidity, drug use, risk tools, detoxification, identification tools, prediction, alcohol withdrawal syndrome (AWS), severe alcohol withdrawal (SAW), seizure, alcohol related seizures, delirium tremens, DT`s. (Outcome)
Databases searched	CINAHL, MEDLINE, MEDLINE in process, Psychinfo, Cochrane database of systematic reviews, EMBASE classic and EMBASE
Part of journals searched	First stage involved screening of title and abstract for relevance and in the second stage, the main text was reviewed against the inclusion and exclusion criteria
Years of search	1989 to 2017
Language	English language only
Types of studies to be included	Quantitative and qualitative studies
Inclusion criteria	Humans over 16 years of age admitted to a general hospital and ICD, DSM or diagnostic coding of ADS, severe AUD, DT`s, ARS or AWS
Exclusion criteria	Children and research carried out in mental health/psychiatric care environments because psychiatric symptoms can often mimic alcohol withdrawal syndrome

SEVERE ALCOHOL WITHDRAWAL SYNDROME: REVIEW OF THE LITERATURE

ABSTRACT

PURPOSE: This review set out to identify published literature from a general hospital setting that may highlight variables implicated in the development of severe alcohol withdrawal syndrome (SAWS) in patients who have alcohol dependence syndrome (ADS).

DESIGN/ METHODOLOGY: A systematic literature review was carried out using the electronic databases: MEDLINE, Medline in Process, Cinahl, Embase and PsycINFO from 1989 to 2017. The focus of this search was on English language studies of individuals over 16 years admitted to general hospital with ADS, delirium tremens (DT's), alcohol related seizure (ARS) or alcohol withdrawal syndrome (AWS).

FINDINGS: Of the 205 studies screened, eight met the criteria for inclusion. Six studies were quantitative retrospective cohort and two were retrospective case-control. Six studies investigated risk factors associated with DT's, one examined SAWS and one alcohol kindling. Descriptive analysis was performed to summarize the empirical evidence from studies, were twenty two statistically significant risk factors were found; including reason for admission to hospital, daily alcohol consumption, previous DT's and prior ARS. The last two factors mentioned appeared in two studies.

RESEARCH LIMITATIONS: Further research should consider the quality and completeness of the alcohol history data and competence of staff generating the data in retrospective studies.

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3 **ORIGINALITY/ VALUE:** The paper suggests that the factors linked to SAWS development
4
5 from the literature may not fully explain why some individuals who have ADS develop
6
7 SAWS, and others do not.
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11 **KEYWORDS:** alcohol, general hospital, delirium tremens, alcohol-related seizures, alcohol
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13 withdrawal syndrome
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16 **PAPER TYPE:** literature review
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INTRODUCTION

Alcohol-attributable disease and injury are widespread (Rehm and Imtiaz, 2016). Excessive alcohol consumption contributes to approximately 6% of worldwide deaths and over 5% of health conditions (World Health Organisation, 2014). In Scotland, 6.5% of all deaths for over 16s are attributable to alcohol (ScotPHO, 2018). The severity of alcohol use is depicted within a spectrum of Alcohol Use Disorders (AUDs). AUD is a generic term used to describe a proliferation of outcomes related to alcohol consumption and is considered to be an indicator of the physical and psychological harm caused by drinking (Scottish Government, 2018).

Even though the term alcohol dependence has been replaced in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013) most individuals who had an alcohol admission to acute general hospitals were historically described as consuming alcohol in this manner (James *et al.*, 2012). Despite the term appearing outdated, it is still prevalent in research and practice (Pryce *et al.*, 2017). A consequence and risk of drinking dependently then cutting down or ceasing alcohol abruptly, is the possibility of developing alcohol withdrawal syndrome (AWS). AWS is characterised by a continuum of physical and psychological signs and symptoms, ranging from mild to severe and can be life-threatening (Schuckit, 2014). Munchie *et al.* (2013) describe criteria for mild, moderate and severe alcohol withdrawal syndrome (SAWS) that includes alcohol related seizures (ARS) and delirium tremens (DT's). However, there are no tools available to stratify SAWS risk as to who requires hospital admission in this patient group, with literature lacking agreement (Maldonado *et al.*, 2014). That said, Goodson *et al.* (2014) in their systematic review and meta-analysis identified that a history of ARS, DT's, low potassium

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3 and platelets were associated with SAWS development in individuals who had Alcohol
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6 Dependence Syndrome (ADS) (NICE, 2011; James *et al.*, 2012).
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12 Hospitalisation in those with ADS is confounded by a lack of a tool to stratify risk and the
13
14 likelihood of a person who has ADS experiencing SAWS (NICE, 2011). While several
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16 variables other than DT's and ARS are associated with SAWS development, they present
17
18 little risk in isolation, with escalation of SAWS heightened with multiple factors (NICE,
19
20 2011). This review aims to identify variables in the published literature that can be studied
21
22 further to develop a risk stratification tool that can predict the outcome of SAWS in order to
23
24 improve the management of patients, thus potentially saving healthcare costs and resources.
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32 **METHOD**

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35 A comprehensive search strategy was undertaken to identify primary research studies that
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37 identified routinely collected health data that could predict the risk of SAWS, DT's and ARS
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39 in a general hospital population of patients who have ADS. The electronic databases;
40
41 Medline, Medline in Process, CINAHL (Cumulative Index to Nursing and Allied Health
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43 Literature), Embase and PsycINFO were searched from 1989 to 2017. This starting year was
44
45 selected as it is a seminal date for alcohol withdrawal management with the advent of the
46
47 Clinical Institute Withdrawal Assessment-Alcohol revised (CIWA-Ar) into clinical practice
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49 (Sullivan *et al.*, 1989).
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Inclusion criteria

Inclusion in the systematic literature review included human studies in individuals over 16 years, conducted within a general hospital setting, with ICD, DSM or diagnostic coding of ADS, severe Alcohol Use Disorder (AUD), DT's, ARS or SAWS. Study design included quantitative or qualitative approaches, with any method of data collection. Quantitative studies using observational or randomised controlled trial methods were included.

Search terms

The literature search used a combination of keywords associated with clinical and risk factors attributed with the development of DT's, ARS and SAWS. The Patient Intervention Comparison Outcome (PICO) (Richardson *et al.*, 1995) framework was utilised to help define and concentrate the literature search. The search was limited to English language studies and reference lists were reviewed for additional studies. In addition to this, Google scholar and the latest editions of the journals Alcohol, Alcohol and Alcoholism, Alcoholism: Clinical and Experimental Research, Journal of Studies on Alcohol and Drugs, American Journal of Addiction, Drug and Alcohol Today, British Medical Journal and the Lancet were reviewed to capture any new articles not available in the bibliographic databases searched. Systematic reviews and clinical guidelines will not be included in the review but their reference lists were scanned to identify potentially relevant references not retrieved by the database searches. Clinical guidelines, epidemiological studies as well as discussion/opinion papers were excluded. The literature search strategy is provided in Table 1.

TABLE 1 ABOUT HERE

Study design

Quantitative studies were unanimous within the literature and included, primarily observational, either from retrospective case notes, retrospective cohort or retrospective case-control. The primary condition of study participants was an ICD code of alcohol dependence or a DSM code of severe AUD. Study participants could also have a diagnostic coding of DT's, ARS or AWS. Secondary or co-morbid conditions were mainly liver cirrhosis or a non-stated physical illness. The main focus of the studies was the assessment, monitoring and treatment of SAWS symptoms. Routinely presented factors associated with SAWS risk and prediction risk.

One reviewer screened the title and abstracts, where available, of bibliographic records retrieved by the searches. Full-text copies of all papers reporting potentially relevant trials were retrieved. All of the studies identified for inclusion were reviewed individually by two reviewers and to review the literature pool. Two reviewers agreed on the final list of studies for inclusion in the review.

Data extraction

One reviewer extracted the data from the included studies using a standard data extraction form. The initial data extraction form included ADS/ severe AUD classification, qualifications of staff undertaking assessment and research, descriptive statistics about the study population, any co-morbid physical or mental health, method used, AWS intervention and guidance, outcome predictors and limitations of study. This was cross-checked by a second reviewer. Inter-rater reliability was tested on a random sample of 10% of the studies

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3 with the wider research team resolving any disagreements. Descriptive analysis of the
4 combined findings was performed to summarize the empirical evidence from studies.
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10 11 **Quality assessment of studies**

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15 The Reporting of studies Conducted using Observational Routinely-collected health Data
16 (RECORD) (Benchimol *et al.*, 2015) was utilised to support the quality of studies used in this
17 review. RECORD supports evaluation of retrospective studies using routinely collected
18 health data to determine' strengths and weaknesses and facilitate the sound interpretation and
19 application of the results (Nicholls *et al.*, 2015). No studies were rejected for low quality.
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30 **RESULTS**

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33 The initial search identified a total of 853 articles, reducing to 205 after the exclusion of
34 duplicates. After title and abstract scanning; one-hundred and fifty six articles were rejected
35 (focusing on management of ARS n=84, DT`s n=24, SAWS n=42, animal studies n=6). Full-
36 text articles were retrieved for the remaining 49 studies and assessed for eligibility against the
37 inclusion criteria. The search and screening process is shown in Figure 1 adapted from Moher
38 *et al.* (2009).
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48 **FIGURE 1 ABOUT HERE**

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51 Twelve articles were then excluded as they investigated specialised blood results and their
52 relationship with ARS. These bloods; homocysteine (HCY), carbohydrate deficient
53 transferrin (CDT), oxidative DNA and prolactin serum levels are not routinely collected in
54 emergency departments. Eleven articles were excluded as they were not conducted within a
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3 general hospital, six were not primary research studies, five had no ICD, DSM or diagnostic
4 coding of ADS, severe AUD, DT's, ARS or AWS and seven were not included because
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6 research in these articles focused primarily on the evaluation of a tool for assessing SAWS
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8 symptoms. Eight articles were found to fit the inclusion criteria and were incorporated into
9
10 the systematic review. The eight included articles are outlined in Table 2.
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14 15 **TABLE 2 ABOUT HERE** 16

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18 All studies reviewed were quantitative in design and used a retrospective means for collecting
19 data using either a retrospective case-control or cohort methodology, in an acute general
20 hospital setting. Studies ranged in size from just over 50 participants to nearly 7,000. All but
21 one study (Lee *et al.*, 2005) (South Korea) was carried out in Western countries (Germany,
22 Spain, France, US). The population studied from the literature was overwhelmingly white
23 (68%) and male (88%) with a mean participant age of between 37-55 years.
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36 Of the eight studies reviewed, six concentrated on the SAWS manifestation of DT's (Eyer *et*
37 *al.*, 2011; Ferguson *et al.*, 1996; Lee *et al.*, 2005; Lukan *et al.*, 2002; Monte *et al.*, 2010), one
38 (Menecier *et al.*, 2008) analysed factors associated with SAWS and Booth and Blow (1993)
39 investigated risk factors and the kindling effect. All studies were retrospective, ranging from
40 12 months (Wright *et al.*, 2006; Ferguson *et al.* 1996; Booth and Blow, 1993) to 108 months
41 (Eyer *et al.*, 2011). The majority of studies defined ADS using ICD and DSM except Lukan
42 and colleagues (2002) who utilised the trauma registry diagnostic coding in the United States.
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44 All patients who developed DT's, SAWS and alcohol kindling had a diagnosis of ADS.
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3 Two studies used an alcohol withdrawal symptom tool to identify SAWS. Menecier *et al.*
4 (2008) suggested SAWS at a Cushman (Cushman *et al.*, 1985) score of greater than or equal
5 to eight at the emergency department ($p=0.002$) and Eyer *et al.* (2011) associated SAWS with
6 a highest Clinical Institute Withdrawal Assessment-Alcohol revised (CIWA-Ar) (Sullivan *et*
7 *al.*, 1989) score above 15 (OR, 1.23; 95% CI, 1.1- 1.4, $p<0.001$). The Cushman score is used
8 to assess the severity of AWS via a number of clinical characteristics such as pulse, systolic
9 blood pressure (SBP), respiratory rate and tremor. CIWA-Ar is a validated tool used to assess
10 and treat AWS through a number of variables, including nausea and vomiting, tremor,
11 paroxysmal sweats, anxiety and agitation. While the other studies did not quantify a measure
12 of SAWS, they did recognise DT's in accordance to ICD or DSM classification. Eyer *et al.*
13 (2011) used a symptom-triggered medication regimen and Menecier *et al.* (2008) a fixed
14 dosing one. Benzodiazepines were the treatment of choice with Booth and Blow (1993)
15 incorporating anti-convulsion medication for the prevention of seizures. Interestingly, Monte
16 *et al.* (2010) used ethyl-alcohol as a treatment of choice.

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39 The eight studies (Eyer *et al.*, 2011; Ferguson *et al.*, 1996; Lee *et al.*, 2005; Lukan *et al.*,
40 2002; Monte *et al.*, 2010; Menecier *et al.*, 2008; Booth and Blow, 1993) looking at DT's,
41 SAWS and alcohol kindling investigated the statistical significance of 69 variables, of which
42 43 were only present in one study. The number of variables investigated within each study
43 ranged from 6 to 32. The demographic variables of interest in the development of DT's,
44 SAWS and alcohol kindling were employment, housing and gender. Race was investigated in
45 four studies and Lukan *et al.* (2002) identified white race as statistically significant in the
46 development of DT's (OR 2.67; 95% CI: 1.44-4.97: $p=0.002$), though Ferguson *et al.* (1996),
47 Wright *et al.* (2006) and Menecier *et al.* (2008) did not. Seven out of eight studies evaluated
48 the relationship between age and the development of DT's, SAWS and alcohol kindling with
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3 the exception of the Menecier *et al.* (2008) study. Statistical significance and the
4 development of alcohol kindling and DT's was statistically associated with age in the Booth
5 and Blow (1993) ($p<0.0001$) and Lukan *et al.* (2002) ($p<0.001$) studies, although the
6 parameters differed.
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16 Six studies evaluated a number of laboratory diagnostic tests in predicting the risk of DT's,
17 SAWS and alcohol kindling (Ferguson *et al.*, 1996; Lee *et al.*, 2005; Wright *et al.*, 2006;
18 Menecier *et al.*, 2008; Monte *et al.*, 2010; Eyer *et al.*, 2011). Only Eyer *et al.* (2011)
19 identified laboratory diagnostic tests as statistically significant; potassium (OR/1mmol; 0.33;
20 95% CI: 0.17-0.65: $p=0.001$) and platelets (OR/100; 0.42; 95% CI: 0.26-0.69: $p=0.001$) were
21 associated with SAWS. The physiological observations of SBP, diastolic blood pressure
22 (DBP), pulse rate, Glasgow Coma Scale (GCS) and temperature were investigated in five
23 studies (Ferguson *et al.*, 1996; Lukan *et al.*, 2002; Lee *et al.*, 2005; Monte *et al.*, 2010; Eyer *et al.*
24 *et al.*, 2011). Monte *et al.* (2010) found that at greater than 150 mmHg, SBP was associated
25 with DT's (OR 1.9; 95% CI: 1.1-3.8: $p=0.03$). In addition, Lee *et al.* (2005), associated a
26 pulse rate greater than 100 beats per minute with the development of DT's (OR 4.16; 95%
27 CI: 2.03-8.51: $p<0.0001$), whereas Monte *et al.* (2010) and Eyer *et al.* (2011) found no
28 association. A temperature greater than 38 °C was identified as statistically significant in the
29 development of DT's (OR 1.9; 95% CI: 1.05-3.5: $p=0.01$) in the study by Monte *et al.*
30 (2010).
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55 The predictability of co-morbidity was evaluated in six studies (Ferguson *et al.*, 1996; Lukan
56 *et al.*, 2002; Lee *et al.*, 2005; Menecier *et al.*, 2008; Monte *et al.*, 2010; Eyer *et al.*, 2011).
57 Ferguson *et al.* (1996) investigated co-morbidity as a single variable and Lee *et al.* (2005) as
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3 acute and chronic illness. The study by Ferguson *et al.* (1996) reflected co-morbidity as
4 statistically significant in the development of DT's (OR 5.1; 95% CI: 2.07-12.55: $p=0.0004$),
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6 Eyer *et al.* (2011) identified brain lesion as statistically significant (OR 5.8; 95% CI: 2.6-
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8 12.9: $p<0.001$), whereas Lukan *et al.* (2002) recognised motor vehicle collision (OR 0.50;
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10 95% CI: 0.32-0.78: $p=0.002$) as a factor in safeguarding against DT's.
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18 Among the variables associated with problematic alcohol use, the predictability of previous
19 DT's on the outcome of DT's and SAWS was investigated in five studies (Ferguson *et al.*,
20 DT's on the outcome of DT's and SAWS was investigated in five studies (Ferguson *et al.*,
21 1996; Lee *et al.*, 2005; Wright *et al.*, 2006; Menecier *et al.*, 2008; Eyer *et al.*, 2011). A
22 history of DT's was statistically significant in the development of DT's in the studies by Lee
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24 1996; Lee *et al.*, 2005; Wright *et al.*, 2006; Menecier *et al.*, 2008; Eyer *et al.*, 2011). A
25 history of DT's was statistically significant in the development of DT's in the studies by Lee
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27 1996; Lee *et al.*, 2005; Wright *et al.*, 2006; Menecier *et al.*, 2008; Eyer *et al.*, 2011). A
28 history of DT's was statistically significant in the development of DT's in the studies by Lee
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30 1996; Lee *et al.*, 2005; Wright *et al.*, 2006; Menecier *et al.*, 2008; Eyer *et al.*, 2011). A
31 history of DT's was statistically significant in the development of DT's in the studies by Lee
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33 1996; Lee *et al.*, 2005; Wright *et al.*, 2006; Menecier *et al.*, 2008; Eyer *et al.*, 2011). A
34 history of DT's was statistically significant in the development of DT's in the studies by Lee
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36 1996; Lee *et al.*, 2005; Wright *et al.*, 2006; Menecier *et al.*, 2008; Eyer *et al.*, 2011). A
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39 1996; Lee *et al.*, 2005; Wright *et al.*, 2006; Menecier *et al.*, 2008; Eyer *et al.*, 2011). A
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42 1996; Lee *et al.*, 2005; Wright *et al.*, 2006; Menecier *et al.*, 2008; Eyer *et al.*, 2011). A
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45 1996; Lee *et al.*, 2005; Wright *et al.*, 2006; Menecier *et al.*, 2008; Eyer *et al.*, 2011). A
46 history of DT's was statistically significant in the development of DT's in the studies by Lee
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48 1996; Lee *et al.*, 2005; Wright *et al.*, 2006; Menecier *et al.*, 2008; Eyer *et al.*, 2011). A
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51 1996; Lee *et al.*, 2005; Wright *et al.*, 2006; Menecier *et al.*, 2008; Eyer *et al.*, 2011). A
52 history of DT's was statistically significant in the development of DT's in the studies by Lee
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54 1996; Lee *et al.*, 2005; Wright *et al.*, 2006; Menecier *et al.*, 2008; Eyer *et al.*, 2011). A
55 history of DT's was statistically significant in the development of DT's in the studies by Lee
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57 1996; Lee *et al.*, 2005; Wright *et al.*, 2006; Menecier *et al.*, 2008; Eyer *et al.*, 2011). A
58 history of DT's was statistically significant in the development of DT's in the studies by Lee
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60 1996; Lee *et al.*, 2005; Wright *et al.*, 2006; Menecier *et al.*, 2008; Eyer *et al.*, 2011). A
history of SAWS was statistically significant in the development of alcohol kindling
($p<0.001$). Booth and Blow (1993) also recognised previous detoxification, and ARS as
associated with alcohol kindling ($p<0.001$), whereas Wright *et al.* (2006) found no
association between previous detoxification and DT's ($p>0.05$). Additionally, Ferguson *et al.*
(1996), Monte *et al.* (2010) and Eyer *et al.* (2011) recognised no association between a
history of SAWS and the development of DT's, while Menecier *et al.* (2008) found no
association between previous SAWS and the development of SAWS. However, previous
ARS was associated with DT's in the study by Monte *et al.* (2010) (OR 2.2; 95% CI: 1.2-3.8:
 $p=0.0005$) but not in the study by Eyer *et al.* (2011) or the Menecier *et al.* (2008) study of
SAWS.

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3 Variables recognised as the consequence of problematic alcohol use and their association
4 with DT`s, SAWS and alcohol kindling showed inconsistency. The quantity of alcohol
5 consumed, family history of alcohol use and length of addiction years showed no association
6 with DT`s, SAWS and alcohol kindling. Ferguson *et al.* (1996) identified that time since last
7 drink was statistically significant in the development of DT`s (OR 1.3; 95% CI: 1.09-1.61:
8 $p=0.047$), although Lee *et al.* (2005) and Monte *et al.* (2010) did not find this link. ARS as a
9 reason for admission to hospital, increased the risk of ARS during admission in the study by
10 Eyer *et al.* (2011) (OR, 2.6; 95% CI, 1.4- 4.8, $p=0.002$), while being admitted with AWS did
11 not (Monte *et al.*, 2010; Eyer *et al.*, 2011). Menecier *et al.* (2008) recognised that symptoms
12 of AWS captured by a Cushman score of greater than or equal to eight in the emergency
13 department was associated with the development of SAWS ($p=0.002$), although Eyer *et al.*
14 (2011) did not find this link with AWS score at the emergency department.
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DISCUSSION

The summary of the empirical evidence and statistical analysis presented by studies in the systematic literature review identified 22 variables as statistically significant (Table 2). The statistically significant variables included; age, race, co-morbidity, consequence of problematic alcohol use, physiological observations and laboratory diagnostic tests, although only previous DT's (Lee *et al.*, 2005; Wright *et al.*, 2006) and ARS (Booth and Blow, 1993; Monte *et al.*, 2010) were found in more than one study. Different health databases, variability in quality assurance processes and lack of information as to whether data was coded before or after upload to the database or at all, within studies might compromise findings (DesRoches *et al.*, 2013).

Demographic data as an indicator of DT's, SAWS and alcohol kindling risk, was only significant for age (Booth and Blow, 1993; Lukan *et al.*, 2002) and race (Lukan *et al.*, 2002). Gender showed no association with DT's, SAWS and alcohol kindling (Monte *et al.*, 2010; Eyer *et al.*, 2011), although this review consisted of studies comprising predominantly of males. In addition, while Lukan and colleagues (2002) identified white race as associated with SAWS, they failed to provide information on whether the comparator was non white or different ethnic groups.

The relationship between age and SAWS was variable in the systematic literature review. Although it is assumed that age is an indicator of SAWS risk given that advanced age suggests more years of drinking, this was not found in the general hospital population within the systematic literature review, but evident in other populations. Booth and Blow (1993) in

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3 their study of veterans identified age as statistically significant ($p < 0.001$) in alcohol kindling,
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5 whereas Wright *et al.* (2006) in their study of veterans did not find this relationship.
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7 Nonetheless, it is difficult to discount this relationship in the veteran population when the
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9 Booth and Blow (1993) study involved a sample of 6,818 from throughout the United States
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11 of America and Wright *et al.* (2006) a sample of 56. In addition, problematic alcohol use is
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13 more prevalent in the military than the general population especially in the event of post
14
15 traumatic stress disorders (PTSD) (Teeter *et al.*, 2017). While the link with older age is also
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17 evident in the trauma population (Lukan *et al.*, 2002) the population were considerably
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19 younger and therefore older age set at a lower level (greater than 40 years). A similar finding
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21 has previously been reported in trauma patients (Parran *et al.*, 1995).
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31 Uncertainty between co-morbidity and alcohol complications was also evident. Interestingly,
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33 while the co-morbidity most associated with alcohol use is alcohol liver disease (ALD)
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35 (NICE, 2011; WHO, 2014), ALD was not a component of most studies in the review. The
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37 non-inclusion of ALD may be due to a low prevalence within the study populations, while
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39 liver function tests may be a better measure of acute and chronic liver injury due to alcohol
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41 use. Nonetheless, liver function blood tests identified similarities between the group who
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43 developed and did not develop complications of alcohol use.
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51 The earliest symptoms of AWS are a result of over activity of the autonomic nervous system,
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53 causing elevation of the physiological markers of SBP, DBP and pulse rate (McKeon *et al.*,
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55 2008; Carlson *et al.*, 2012). The systematic literature review for the most part failed to
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57 support this, although when associated with alcohol complication, the recorded observations
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59 exceed normal levels in the studies by Lee *et al.* (2005) and Ferguson *et al.* (1996). The lack
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3 of association between physiological markers and SAWS in the reviewed studies may be a
4 consequence of unreported confounding factors such as pharmacological intervention.
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6 Pharmacological intervention for co-morbidity such as hypertension may negate the body's
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8 natural response to AWS maintaining a normal blood pressure.
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16 The analysis of whether a history of complicated alcohol events; DT's, ARS and SAWS were
17 a factor in developing future events, like the other results, is inconstant. Alcohol history is
18 mainly self-reported and subject to issues of recall, while the terms DT's and SAWS are often
19 misrepresented or over used in the alcohol literature (NICE, 2011; Eyer *et al.*, 2011). In this
20 review only previous DT's and ARS were found to be associated with the development of
21 DT's (Lee *et al.*, 2005; Wright *et al.*, 2006) and ARS (Booth and Blow, 1993; Monte *et al.*,
22 2010) in more than one study.
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36 The studies within the systematic literature review all propose that the patients within the
37 studies are subject to an alcohol detoxification and the alcohol kindling theory infers that the
38 number of detoxification events increase a person's risk of SAWS that includes DT's and
39 ARS (Rathlev *et al.*, 2006). However, if detoxification is aimed at reducing the psychological
40 trauma and neurological adaptation associated with the need to maintain homeostasis
41 (Martinotti, 2009; Heymann *et al.*, 2010), then previous DT's, ARS and SAWS suggest an
42 experience and consequential adaptation (Becker, 2008). Therefore, development of alcohol
43 complications in the context of medically assisted detoxifications proposes neurological
44 adaptation regardless of symptom amelioration and possible under treatment of the preceding
45 AWS (The Royal College of Physicians, 2010). The concept of under treatment is difficult to
46 exclude in the Booth and Blow (1993), Lee *et al.* (2005) and Monte *et al.* (2010) studies were
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3 no tools to influence alcohol withdrawal treatment were evident, an omission not found in the
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5 studies were previous DT's and ARS were not associated with DT's and ARS development
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7 (Menecier *et al.*, 2008; Eyer *et al.*, 2011). The concept of poor alcohol management in the
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9 acute hospital is recognised (McKeon *et al.*, 2008; Swift *et al.*, 2010; Sutton and Jutel, 2016)
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11 and difficult to discount in the systematic literature review where the majority of studies
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13 investigated DT's within alcohol detoxification treatment.
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21 The data collection period within studies ranged from 1-16 years, and the exploration of
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23 different health databases presented difficulty assuring consistency and quality assurance.
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25 The studies presented no information on when and if the data abstracted from the databases
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27 was coded. In addition, no studies presented information on the competence levels of the staff
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29 that generated the primary data, although poor alcohol assessment in the general hospital
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31 environment is frequently reported in studies (The Royal College of Physicians, 2010; NICE,
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33 2011).
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41 While the results presented within the systematic literature review identified a lack of
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43 consensus in the variables that contributed to alcohol complications, there was consistency in
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45 the limitations presented by studies. Limitations included; sub-optimal alcohol history,
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47 missing data, poor SAWS and DT diagnosis, inconsistent treatment and failure to use
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49 screening and treatment tools. Other than a previous history of DT's and ARS the systematic
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51 literature review provided no clarity to other factors that increased the risk of developing
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53 alcohol complications; DT's, ARS and alcohol kindling in the acute hospital. However, the
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55 systematic literature review provided a pool of statistically significant variables from single
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3 studies that in combination warrant further investigation in the goal of developing a risk
4 stratification tool for AWS.
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11 There are a number of limitations to this review. Although a comprehensive search was
12 undertaken, only studies presented in English were included. In addition, the heterogeneous
13 nature of studies and definition of variables such as drinking patterns prevented the
14 possibility of undertaking a meta-analysis of results. Bias was evident within studies where
15 only selected variables from the literature were included, while the retrospective nature of
16 studies and use of routinely collected data limited the rigour and generalisability of results.
17 Therefore, the extensive variability and lack of commonality in the factors identified as
18 significant in the development of alcohol complications requires further exploration. We
19 propose that future research into risk variables and alcohol complications should include;
20 greater numbers of females, a greater divergence of participant ethnicity, alcohol history data
21 captured by clinical experts in alcohol assessment, and investigation of all documented
22 statistically significant variables.
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Drugs and Alcohol Today

TABLE 2. Summary table of articles reviewed

<i>Study</i>	<i>Study design</i>	<i>Intervention target (ADS/ severe AUD classification)</i>	<i>Number and co-morbid physical/ psychological health. Place of research</i>	<i>Intervention and treatment guidance</i>	<i>Prediction of significance / outcomes</i>
Booth and Blow (1993)	Retrospective case note review	ICD-9	(n=6,818; males only). 75.4 Caucasian 75.4%; African American 20.4%; Hispanic 3%; Native American 1.2%. Data from US Veterans Affairs Department. United States.	Alcohol detoxification – intervention not specified. Guidance protocol not specified	1. Previous alcohol detoxification (p<0.01). 2. Previous SAWS (p<0.001). 3. Previous ARS (p<0.001). 4. Older age (p<0.0001)
Eyer <i>et al.</i> , (2011)	Retrospective cohort study	ICD-10	(n=827). Physical illness (liver cirrhosis, pancreatitis).	Benzodiazepines, clomethiazole. Alcohol Withdrawal Scale (AWS) and CIWA-Ar.	5. Maximum AWS score during admission (OR, 1.23: 95% CI, 1.1- 1.4, P<0.001), 6. Presence of structural brain lesion (OR, 6.5: 95% CI, 3.0- 14.1, p<0.001) 7. ARS as reason for admission (OR, 2.6: 95% CI, 1.4- 4.8, p=0.002) are associated with risk of ARS. 8. Low potassium (OR, 0.33: 95% CI, 0.17- 0.65, p=0.001), 9. Low platelets (OR, 0.42: 95% CI, 0.26- 0.69, p=0.001) 10. Brain lesion (OR, 5.8: 95% CI, 2.6- 12.9, p<0.001) are associated with an increased risk of DT's
Ferguson <i>et al.</i> , (1996)	Retrospective cohort study	ICD-9	(n=200; males 85%). Caucasians 57%. Physical illness.	Benzodiazepines. Protocol not specified.	11. Concurrent acute medical illness (OR, 5.1:95% CI, 2.7-12.55, p=0.0004). 12. Two or more days since last drink (OR, 1.3:95% CI, 1.09-1.61 p=0.0047).
Lee <i>et al.</i> , (2005)	Retrospective cohort study	DSM-IV	(n=147: males 95.5%). Physical illness.	Benzodiazepines. Protocol not specified.	13 Previous DT's- (OR, 3.990: 95% CI, 1.631- 9.759, p=0.002) 14. increased pulse rate (OR, 4.158: 95% CI, 2.032- 8.511, p<0.0001) associated with risk of DT's
Lukan <i>et al.</i> , (2002)	Retrospective	Trauma registry diagnostic coding	(n=1,855; males 85.6%). Caucasians 72.6%. Trauma patients.	Benzodiazepines. Protocol not specified.	15. Age>40 years (OR, 2.98: 95% CI, 1.97- 4.51, p<0.001), 16. White race (OR, 2.67: 95% CI, 1.44- 4.97, P<0.007), 17. Burn injury (OR, 3.63: 95% CI, 1.46- 9.00, p=0.006) 18. motor vehicle collision as a negative predictor

(OR, 0.50: 95% CI, 0.32- 0.78, p<0.001) are associated with risk of DT's.

19. Cushman score ≥ 8 (P=0.002)

3. Previous ARS (OR, 2.2: 95% CI, 1.2- 3.8, p=0.005). **20.** ≥ 3 (OR, 2.6: 95% CI, 1.04- 6.8, p=0.04), **21.** Temp>38 °C (OR, 1.9: 95% CI, 1.05- 3.5, p=0.03). **22.** systolic BP >150 mmHg (OR, 2.1: 95% CI, 1.1- 3.8, p=0.01) associated with a greater risk of DT's

13. Previous DTs ($X^2=5.77$, dof=1, p=0.016)

Menecier <i>et al.</i> , (2008)	Retrospective study	DSM-IV	(n=182; males 74.7%). Liver cirrhosis and alcoholic pancreatopathy. Specialist outpatients and emergency department referrals to gastroenterology and hepatology departments. France.	Diazepam or oxazepam. Cushman score.
Monte <i>et al.</i> , (2008)	Retrospective cohort study	DSM-IV	(n=436; males 91.3%) Physical illness (liver cirrhosis, steatohepatitis). University teaching hospital. Spain.	Benzodiazepines and ethyl alcohol (wine). No protocol stated.
Wright <i>et al.</i> , (2006)	Retrospective case-control study	ICD-9	(n=56; males 100%). Caucasians 64.2%; African American 32.2%; Native American 3.6%. Acute physical health. United States.	Benzodiazepines, anti-psychotics and anti-epileptics. CIWA-Ar