

Alcohol Use Disorders: Implications for the Clinical Toxicologist

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Abstract

Alcohol use disorders (AUDs) are a health problem of high prevalence in most communities and such problems account for 5% of the total burden of disease worldwide. Clinical toxicologists are commonly required to treat patients having AUDs and associated drug/alcohol-related harm. There have been recent changes to some of the diagnostic criteria (notably in DSM V) relevant to AUDs, with older terms “alcohol abuse” and “alcohol dependence” no longer being classified. AUDs may sometimes not be clearly recognizable and use of evidence-based screening interventions can help identify such conditions and lead to effective brief interventions (e.g. SBIRT programs in emergency departments). AUDs are viewed as chronic disorders of alcohol consumption occurring across a spectrum of severity. While most AUDs are mild to moderate in severity and usually self-limiting conditions, more severe presentations are more commonly encountered by physicians in emergency settings. Hence, clinical toxicologists are more likely to see patients within the more severe form of disorder, at end of the spectrum of AUDs. Among this group of patients, multi-morbidity and particularly high mortality risk exists, and thus they usually require management collaboration with specialist services. Patients with AUDs are most likely to be recognized by a clinical toxicologist in the following scenarios: following acute heavy alcohol ingestion and subsequently developing acute alcohol intoxication (ethanol toxidrome), following accidental or intentional drug overdose where alcohol has also been consumed, following acute alcohol consumption that has been associated with behavioral risk-taking and/or self-harming (e.g. poisoning, envenomation, etc.), when alcohol withdrawal reactions are severe requiring hospitalization and possibly following an adverse drug reaction.

Keywords: Alcohol Related Disorders; Alcohol Deterrents; Alcoholism; Substance Withdrawal Syndrome; Toxicologist

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INTRODUCTION

In 2012, about 5.9% global deaths and 5.1% of the global burden of disease were attributable to alcohol consumption (1). While it appears likely that most people who drink, do so moderately and that their alcohol use is associated with the experience of pleasure, positive social interaction and low risk of adverse outcome, there also appears a dose-response relationship between the amount of alcohol consumed and risk of harm (1-4). Past reports associating modest alcohol consumption with cardio-protective benefits have more recently been questioned (5-7), and rather it may be that only a genetic sub-group is likely to obtain such benefit (8). Patients with alcohol use disorders (AUDs) are commonly male and are overrepresented in the population of patients attending an emergency department (ED) around the world (9-11). Furthermore, AUDs and cigarette smoking are two of the commonest causes of preventable drug-related harm in the world (3). Alcohol is frequently consumed by patients who take drug over-dosage and can contribute to both the etiology and outcome of drug overdose (12,13). Alcohol ingestion has etiological implication in accidental injuries, road trauma, industrial accidents, violence and drowning (14-19) and it has been estimated that between one in seven to one in three ED presentations are alcohol related and many

such presentations are often under-reported (11). Clinical toxicologists are sometimes involved in treating patients with AUDs, particularly in the management of poisoning in an intoxicated patient (possibly an alcoholic), severe alcohol withdrawal reactions (occasionally requiring inpatient care) and sometimes advising on management of an intoxicated patient with suspected poisoning who may be at risk for inappropriate self-discharge. Occasionally, following acute treatment, a toxicologist may be required to assist in formulating an ED discharge plan requiring knowledge about referral options for the patient's further continuing care i.e. knowing how to connect such patients with alcohol rehabilitation services. For all these aforementioned reasons, it is important for the clinical toxicologist to be conversant with AUDs, their prevalence and their acute and chronic management. AUDs etiology, screening and therapeutics has been extensively reviewed elsewhere (20,21) and hence this paper focuses upon those areas likely of interest to the clinical toxicologists.

Alcohol use disorder, description and diagnostics

It is important to note that for the majority of people, an AUD is a temporary condition that, in most cases, does not progress to chronic alcoholism. AUDs are currently recognized as conditions that exist across a spectrum of severity and with reference to the DSM V (22), diagnosed

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Table 1. DSM V Diagnostic Criteria for Alcohol Use Disorder (22)

1. Alcohol is often taken in larger amounts or over a longer period than was intended
2. There is persistent desire or unsuccessful efforts to cut down or control alcohol use
3. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol or recover from its effects
4. Craving or a strong desire or urge to use alcohol
5. Recurrent alcohol use resulting in a failure to fulfil major role obligations at work, school or home
6. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol
7. Important social, occupational or recreational activities are given up or reduced because of alcohol use
8. Recurrent alcohol use in situations in which it is physically hazardous
9. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol use
10. Tolerance defined as either a need for markedly increased amounts of alcohol to achieve desired effect or markedly diminished effect with continued use of the same amount of alcohol.
11. Withdrawal, as manifested by either the characteristic withdrawal syndrome for alcohol or alcohol is consumed to relieve or avoid withdrawal symptoms.

The presence of at least two criteria indicates alcohol use disorder. The grading of severity of alcohol use disorder is defined in terms of the number of criteria present e.g. two or three criteria indicate mild severity, 4 to 5 criteria indicate moderate severity and six or more criteria indicate high severity. (Additionally, the presence or absence of physiological dependence is specified.)

when at least two of eleven criteria are present (Table 1). The more criteria that are present indicates a greater severity of the AUD (22). Diagnostic terminologies like "alcohol abuse" and "alcohol dependence", the former relating to chronic drinking problems correlated with harm and the latter specific to a state where alcohol use is associated with physiological dependence or neuro-adaptation, are no longer defined in DSM V (22,23). Furthermore, a more severe form of AUD associated with increased tolerance to alcohol, risk of withdrawal reactions and reinstatement after a period of abstinence, is additionally specified as having physiological dependence i.e. severe AUDs can exist with or without physiological dependence (22,23). Considering patients having more severe AUDs, it has been estimated that between 40% and 60% of the etiology is related to genetic factors with psychological and social factors contributing the remainder (20,21). In other words, a patient with significant genetic risk (e.g. having a strong family history of alcoholism), lower sensitivity to alcohol effects, growing up in a family where heavy drinking behavior is exemplified and later entering a peer group or a heavy drinking workplace culture, has predictably high risk to develop more severe AUD (20,21,24).

However, it is important to recognize that mild to moderate AUDs are far more prevalent than disorders at the severe form end of the spectrum. Most alcohol-related road accidents, industrial injuries, downings, poisonings, violent and anti-social behaviours occur amongst people with less severe AUDs, such people being far more numerous in the general population (25). While chronic alcoholics (i.e. more severe AUD patients) are overrepresented in the population of patients with cirrhosis of the liver (26), this well recognized form of alcohol related harm affects only a small proportion of the population of people having AUDs. "In other words, the larger population having less severe AUDs account for a

higher burden of morbidity and mortality than the smaller population having more severe AUDs. This phenomenon, termed the "Prevention Paradox" (25), argues that if we are to reduce the mortality and morbidity associated with AUDs, then we should focus on strategies that reduce alcohol consumption across the population and particularly amongst the largest group at risk i.e. those drinking at risky levels (some yet to experience harm). It is therefore argued that doctors should use any opportunity to encourage even occasional heavy drinkers to reduce their alcohol consumption; indeed, medical advice has been shown to have efficacy in reducing patient's alcohol consumption (27).

Much alcohol research over the years has focused on interventions to reduce alcohol-related harm. While patients with more severe AUDs require more intensive intervention, many patients with less severe AUDs (most prevalent) have reasonable potential to respond to brief interventions (28). Such interventions typically comprise of screening and subsequent recognition of the patient at risk. Thereafter, the treating physician provides relevant information to a patient with advice to reduce drinking and finally, arranges follow-up; alternatively, the latter could involve referral for specialized follow-up elsewhere. Because the association between alcohol use and injuries (including poisoning) might be underdiagnosed in many ED presentations (11), screening all "at risk" patients is advocated and thus, Screening, Brief Intervention and Referral into Treatment (SBIRT) programs have developed and showed efficacy (29-31). However, SBIRT programs are not always effective, and they require specialized skills and can be difficult to implement and maintain (32,33). There is now a reasonable evidence-base for many screening methods (29-31) including a single question screening methodology which appears to perform well as a quick, simple and effective screener (34). A commonly used screening test is the Alcohol Use Disorders

Identification Test (AUDIT) which is simple to apply in many settings including the ED (35-39). The patients' score on the AUDIT questionnaire can be the sign of probable severity of the AUD. To take an example, higher scores on AUDIT are more likely associated with severe AUD as well as neuro-adaptation, a state previously described as "alcohol dependence". A shortened format of this test, called the AUDIT-C, which is comprised of 3 questions is available and appears to have comparable efficacy (39,40).

While screening for recent alcohol use with blood levels and breathalyzer testing is often utilized in ED settings, these investigations do not provide correlation with the quantity and frequency of alcohol use (36). Utilizing biomarkers in screening for heavy alcohol consumption has been well reviewed (36,41-44), and while the use of gamma-glutamyltransferase (GGT) level has been considered as a marker for chronic alcohol consumption, there are many factors that lead to changes in GGT levels and heavy alcohol use is only one of them (36,41-44). However, GGT may still be useful as a surrogate marker for chronic alcohol consumption when all other factors are excluded (36,41-44). Carbohydrate Deficient Transferrin (CDT) levels are often elevated in heavy drinkers and CDT testing can be performed well in some settings (45), though the opposite might be true in other settings (46,47). In addition, CDT testing is expensive and perhaps for such reason, it is not widely used. The level of ethyl glucuronide (EtG) detected in blood, urine and other tissues (e.g. hair) has more recently been demonstrated as having good correlation with recent heavy alcohol consumption; however, the availability of this test remains limited (48). As with any other laboratory investigation, results of biological fluid/tissue sampling should always be interpreted in conjunction with information obtained from a thorough history and physical examination in order to best infer diagnostic meaning. Overall, clinical assessment (skilled history and physical examination) and use of questionnaires like AUDIT are more reliable methods for alcohol screening than laboratory tests (36,49).

Acute alcohol poisoning (ethanol toxidrome)

An alcohol intoxicated patient is fairly easily recognized by the characteristic toxidrome features including the feter, slurring speech, an ataxic gait, slowed reflexes and cognition which predictably improves over time in relation to falling blood alcohol levels. When this is not the case, other underlying poisoning and/or pathology should be considered. Severe alcohol poisoning presenting in association with compromised vital signs requires resuscitation, life support and possibly enhanced alcohol elimination by haemodialysis. Agents that partially antagonize some of the depressant effects of alcohol, possibly considered as antidotes (historically referred to as "amethystic" agents after the ancient Greeks believed the amethyst stone possessed detoxifying qualities) like opioid receptor antagonists (e.g. Naloxone) (50), and some GABA_A antagonists (e.g. Ro15-4513) have not proven to be clinically useful. Alcohol appears to mediate much of its sedating effects at a site located on a subtype of the GABA_A receptor consisting of $\alpha 4/6\beta 3\delta$ subunits (51). The experimental agent

Ro15-4513 acts as an antagonist at this receptor site and reverses alcohol-induced sedation in mice (52), and has been used experimentally in animal research over the past 30 years, but its utility in humans has remained unestablished, suggesting it is unlikely to have potential as a therapeutic agent.

For most poisoned patients in ED, immediate management should involve examination to exclude other underlying pathology, concealed alcohol containers, tablets/other substances (possibly sharp objects or weapons) and consideration of the possibility of other concurrent poisonings. When an agitated patient with unknown history is considered as intoxicated, it is important to consider poisoning with psychostimulants and hallucinogens, head injury, psychosis and hypoglycemia (11,53). Performing the examination usually requires the patient to be undressed, provided with a hospital gown and their valuables are secured in a safe place until discharge. Subsequently, if the patient decides unwisely to self-discharge before medically appropriate, the time involved in returning personal effects (and car keys) can be used to call family or if deemed necessary, the police. Routine supportive care for alcohol intoxicated patients includes having the patient nursed in the semi-recumbent position to reduce aspiration risk, provision of regular nursing observations for vital signs, airway protection, wandering and falls risk together with monitoring alcohol elimination by repeated breathalyzer testing. It is also important to recognize that some of these patients may have acquired neuro-adaptation to alcohol (physiological dependence) and therefore be at risk for development of acute alcohol withdrawal as alcohol levels drop. In the latter situation, an alcohol withdrawal scale is recommended to assist nursing observations, monitor the course and severity of the withdrawal reaction and serve as a guide to the use of pharmacological treatment (54).

Alcohol poisoning also produces varying degrees of acute cognitive impairment which complicates the assessment of the underlying mental state. Acute memory disturbance is common during episodes of heavy drinking and this may lead to partial loss of recollection of events during the drinking episode (i.e. only patchy recall may persist) or a total loss of any event memory. This latter condition was sometimes referred to as an "alcoholic blackout" i.e. memory blackout (55), but this term is confusing as a blackout generally has a different meaning especially in an ED context and thus the term probably should be avoided. Moreover, potentially confusing is the DSM V term known as "Alcohol Amnesic Disorder" which appears to specifically relate to persisting memory disorder in alcoholics with thiamine deficiency, otherwise referred to as Korsakoff's Syndrome (22,56). Thiamine deficiency, particularly in chronic alcoholics, may cause acute memory impairment (e.g. Wernicke's encephalopathy) and therefore parenteral thiamine should always be given in such circumstances. Further, abnormality in attention, perception and cognition may be related to acute alcohol exposure especially in high doses (57), and/or an underlying mental disorder (22). AUD and other mental health problems are frequently co-morbid conditions (58-62), so that the presence of both conditions can make it difficult

to determine whether one or both may account for any observed abnormality in a poisoned patient's mental state. Therefore, a psychiatric diagnosis should generally be deferred until after alcohol poisoning wanes (and in alcohol dependent patients, after the withdrawal state abates). In the meantime, poisoned patients with serious mental disorder will need to be treated in accordance with the principle of "duty of care" (63). Ongoing risk for a poisoned patient to self-discharge or abscond from the ED despite having a potentially serious medical/psychiatric status usually warrants the provision of close nursing supervision (e.g. one nurse focused upon one patient), in the safest environment available (e.g. quiet, single room, away from un-supervised exits) and without easy access to alcohol-containing hand-wash dispensers. Some evidence suggests up to fifty percent of patients who self-discharge from medical care are under the influence of drugs or alcohol (64,65). In this respect, it is essential to make every effort to communicate with family/friends and if possible, have them attend and stay with the patient. Inappropriate self-discharge or absconding of a poisoned patient especially when followed by a potentially preventable adverse outcome is likely viewed by concerned family members and/or in the event of death, by a coroner, as an abrogation of "duty of care". Likewise, every effort to deter a poisoned patient from driving should be made and such well documented. In most countries, the law does not require a physician to act as a police officer and restrain a poisoned person intending to drive; however, when efforts to discourage driving fail, "duty of care" may sometimes require the physician to consider notifying the police. Of particular concern are patients with chronic, severe AUD and significant comorbidity who become identified by an ED as a frequent attendee, most of them have high mortality risk and very poor prospects for engagement in treatment (66). In some jurisdictions, compulsory detention in treatment by court orders is available usually when "all other treatment efforts have failed and the patient remains at serious risk" (66-70).

Acquired brain injury is a relatively common comorbidity in many chronic alcoholics and when acutely intoxicated, such alcoholics will be likely to have varying degrees of impairment in their capacity for important decision-making (71-73). When an intoxicated patient appears to make inappropriate decisions that likely place themselves at risk, the mental state examination should include questions that appraise both the patient's capacity to comprehend the risks they are facing and their ability to make an informed decision about their need for treatment. While many of us are sometimes capable of making seemingly irrational decisions, we should be aware that an intoxicated patient's seemingly irrational responses may not always indicate mental incapacity. It is therefore important to focus on the assessment of capacity to make decisions rather than the decision itself (74-77). An intoxicated patient who is acutely confused (i.e. delirium) has become temporarily incapacitated to make decisions about their self-care, and therefore, the attending physician should act according to the "duty of care" imperative (63,74-77). Thereafter, appropriate methods of restraint should be taken into account which

mainly includes the methods posing least risk to patient and staff safety. Restricting patient access to wander and abscond (e.g. use of an electronic alert bracelet), maintaining close supervision, providing comfort and reassurance is always preferable to engaging physical restraint which may be associated with risk of injury to the patient and staff (78,79). Pharmacological means of restraint may pose less risk than physical restraint provided the tranquilizing drugs selected have least risk for adverse interaction, over-sedation and respiratory compromise. Antipsychotics having less anticholinergic activity like droperidol or olanzapine are suggested to be used judiciously in such circumstances (79,80).

Alcohol has vasodilator effects and can increase heart rate. Hence, alcohol consumption is a risk factor for atrial fibrillation (81). Acute, high alcohol dose exposures are usually associated with tachycardia and some individuals appear to be more vulnerable to supra-ventricular tachycardia typically during or following an alcohol binge; the latter is sometimes referred to as the "holiday heart syndrome" (82). This condition is usually self-limiting but occasionally may require acute treatment with agents like β -blockers or calcium-channel blockers (82,83). Arrhythmias in chronic alcoholics should prompt consideration to investigate for alcoholic cardiomyopathy which is typically a dilated form of cardiomyopathy; and in the early stages of development, atrial enlargement may lead to increase in supra-ventricular tachycardia. Alcoholic cardiomyopathy is diagnosed only after hemochromatosis and other causes of cardiomyopathy have been excluded. It is worth noting that this type of cardiomyopathy may improve with alcohol abstinence (84-86).

Acute alcohol withdrawal and associated conditions

In the situation wherein an intoxicated patient is known or suspected to maintain daily alcohol intake and be physiologically alcohol dependent, their acute management plan needs to include ongoing assessment for emergent signs of alcohol withdrawal. This process is assisted by utilizing evidence-based alcohol withdrawal scales which are used to identify withdrawal signs and to score severity, thereby guiding the use of pharmacotherapy. Longer acting benzodiazepines are recommended as first line agents (when medical treatment is indicated), because of their proven safety and efficacy (87-90). Many severely intoxicated patients (typically adolescents) may have had heavy episodic drinking or "binge-drinking" rather than being alcohol dependent. Such patients are therefore not anticipated to later develop acute alcohol withdrawal as their state of intoxication wanes (20,21,91).

Mostly, alcohol withdrawal is of mild to moderate severity and does not require specific medical treatment and many patients manage their withdrawal symptoms at home while some attend non-medical detoxification units wherein supportive care alone and occasionally even treatments such as acupuncture may provide symptom relief (92). Acute and more severe alcohol withdrawal is a hyper-adrenergic state driven by the locus coeruleus which is further exacerbated by brain exposure to up-regulated glutaminergic tone (possibly an adaptive consequence of chronic heavy alcohol use that

contributes to tolerance when drinking), activation of the hypothalamic-pituitary-adrenal axis (stress response) and a variety of other acute neuro-chemical disturbances accounted for disorders of sleep and mental state (90,93,94). Hence, alpha-2 adrenergic antagonists like clonidine, lofexidine and dexmedetomidine (94,95), and beta-blockers such as propranolol and atenolol have been found useful adjuncts in treating more severe alcohol withdrawal reactions (96,97). The aforementioned agents are also used in combination with benzodiazepines in cases of alcohol withdrawal refractory to benzodiazepines alone (98).

Patients who have physiological alcohol dependence may face withdrawal symptoms on a daily basis and thus the experience of withdrawal symptoms alone is unlikely to prompt a need to seek medical attention. However, an acute medical condition which interrupts daily drinking often leads to presentation at the ED, for example, acute gastritis or severe gastro-esophageal reflux disease possibly with haematemesis, protracted vomiting and consequent electrolyte disorders like hypokalemia, hyponatremia and hypomagnesaemia. Hypomagnesaemia is also a common finding in chronic alcoholics due to malnutrition and heavy drinking-related urinary magnesium losses (63,87-90). Alcoholic ketoacidosis is uncommon but more likely diagnosed in adult heavy drinkers with recent poor food intake and persistent vomiting. This condition is identified by an elevated anion gap, elevated ketones (particularly β hydroxybutyrate which is undetectable by urine dipstick testing), metabolic alkalosis and volume depletion (99). Recently, severe cases of alcoholic ketoacidosis have been reported to be associated with visual disturbances (100). Treatment involves fluid resuscitation and correction of glycogen depletion and nutritional deficiencies; though unlike with diabetic ketoacidosis, rarely requires insulin therapy (101).

In general, patients with physiological alcohol dependence are less likely to present with confusion purely related to poisoning, probably because of having higher central tolerance, and therefore other possible causes for confusion need to be taken into account. Possibilities include deterioration in liver function, an occult head injury, a recent seizure with prolonged post-ictal confusional state, concurrent poisoning with other agents and/or acute Wernicke's Encephalopathy (WE) (11,53,54,63,90,102). The latter condition is largely expected in alcoholics who have not been eating or drinking for more than a week, have had significant recent weight loss and have possibly certain genetic and racial predispositions (102-104). Chronic heavy alcohol consumption is associated with reduced thiamine intake, reduced absorption, reduced hepatic uptake and storage and also reduced brain utilization (105,106). It has been reported that the majority of WE episodes are not recognized possibly because physicians rely on the appearance of the classic triad of ophthalmoplegia, ataxia and confusion with short-term memory deficiency (102,103,107). However, more commonly, WE presents clinically as an acute confusional state or with only one or two features of the classic triad. The diagnostic criteria proposed by Caine et al (108), appear to have reasonable

diagnostic accuracy; however, because diagnostic uncertainty may persist, it is now generally advocated to provide thiamine to any patient deemed to be at risk of deficiency. Typically recommended replacement dose of thiamine is 100-300 mg intravenously continued by parenteral therapy daily until the patient can return to normal feeding (102,103,109). It is also essential to correct any magnesium deficiency state because thiamine requires magnesium as a cofactor in functioning (110). Some alcoholics may present with serious malnourishment and be at risk for re-feeding syndrome although in one recent study, this condition was considered to be quite uncommon (111).

More severe alcohol withdrawal is more likely to occur in patients attending hospital ED who have a past history of previous severe alcohol withdrawal and patients with concurrent acute medical/surgical/psychiatric illness which may further exacerbate adrenergic activity (63,87-90,98,112). Complications of severe alcohol withdrawal include seizures, arrhythmia, falls, hallucinosis and delirium; when the latter occurs, it is typically transient and usually lasts for 24 to 48 hours, but often lasts longer in patients with underlying dementia (75,112,113). Many complications are preventable by early provision of benzodiazepines, usually with longer acting agents like diazepam or chlordiazepoxide (or oxazepam which does not require P450 pathways for metabolism when liver disease poses concerns), in addition to supportive care and careful consideration of underlying conditions like volume dehydration, electrolyte disturbances, thiamine deficiency and anxiety (63,87-90,98,112,113). Alcohol withdrawal scales (AWSs) were originally developed for use by skilled nurses to monitor the progress of the withdrawal state and its response to benzodiazepine treatment (114). AWSs are not diagnostic tools and such use has been associated with adverse events such as delaying the diagnosis of a serious underlying condition possibly because not only alcohol withdrawal but also other conditions that can increase adrenergic activity such as myocardial ischemia, pancreatitis, sepsis, etc. may account for the elevated AWS score (63,87-90,98,112,113).

Chronic heavy alcohol consumption has an established dose-related exposure risk for the occurrence of seizures, possibly more in those with genetic vulnerability, and poses increased risk for the occurrence of status epilepticus even following the first episode of seizure (115-117). Acquired alcohol-related brain injury is another cause of seizures in chronic alcoholics, including seizures that occur outside the alcohol withdrawal period, which in some occasions these seizures are representative of post-traumatic epilepsy (118). While alcohol-related seizures are the commonest seizures occurring in alcoholics, in an ED setting, secondary causes always should be considered e.g. hypoglycemia, head trauma, sepsis, co-ingested drugs and non-adherence to anti-epileptic medication (115-121). Seizures that occur in alcoholics soon after the reduction or cessation of drinking are referred to as "alcohol withdrawal triggered seizures". These seizures typically occur between 6 to 48 hours after the last drink. They are brief in duration, generalized (non-focal), self-limiting (non-recurring) and generally do not

require further neurological investigation (119-121). However, treating withdrawal seizures is recommended in order to reduce the risk of post-ictal delirium, further seizures and possible status epilepticus (119-121). Studies done on patients with withdrawal admitted to EDs have shown that these seizures do not respond well to commonly used anticonvulsant therapy (121-123), and instead, benzodiazepine treatment for the underlying cause, the alcohol withdrawal state, is recommended (63,87-90,121). Some evidence suggests lorazepam has better efficacy in preventing recurrent withdrawal seizures during an episode (121). Most patients recover uneventfully after alcohol withdrawal seizure(s) and can be discharged from the ED after a 4 to 6 hour period of observation (121). However, a minority of patients, especially those with underlying brain injury or dementia, can develop post-ictal delirium requiring hospitalization (124). It is recommended to advise all patients who have had alcohol withdrawal seizure(s) not to drive until assessed by a neurologist or an addiction medicine specialist (63,87-90). Delirium Tremens (DT) which has been characterized by delirium, severe tremors, diaphoresis and other features of autonomic instability, sometimes follows alcohol withdrawal seizure(s) (124). DT typically occurs several days after alcohol withdrawal commences and is uncommon nowadays probably because many hospitalized alcoholics receive early treatment for anticipated alcohol withdrawal (63,125,126). When diagnosed, DT requires prolonged supportive treatment and remains a condition with significant morbidity and mortality risk (125-127).

The role of alcohol in other poisonings

Alcohol is a common co-ingestant in many cases of accidental and/or intentional drug overdose, especially in men and sometimes may be consumed accidentally with toxic alcohols (128-131). Even low levels of alcohol consumption in social drinkers reduce anxiety and frontal lobe driven behavioral inhibition (132). It has now been well established that alcohol consumption increases the risk for disinhibition and therefore increases impulsivity particularly after heavy alcohol consumption (132,133). This disinhibition and impulsivity is likely to be a contributing factor for risk taking and self-harming behaviors as in sudden drug overdose. Moreover, heavy and particularly chronic alcohol consumption has depressant effects on mood and some patients appear to be more vulnerable to this effect than others. Such alcohol induced mood disorder (discussed below) can be accompanied by major depressive symptoms including suicidal ideation with the risk of suicidal attempt as a result of enhanced disinhibiting effects of high blood alcohol level. In many cases of intentional drug overdose, the patient has initially consumed alcohol which likely results in disinhibition, and as drinking progresses, it potentially increases the chance of swallowing multiple tablets or other toxic substances (11,128-131). Likewise, drinking followed by disinhibition and potentially acute memory impairment (55,57), can pose risk for accidental overdose when the drinker has multiple medications to self-administer. This also may add risk for misinterpretation of medication labeling and warnings.

Drug overdose when combined with heavy alcohol

ingestion poses increased risk for aspiration to occur because sedation effects may impair airway protection and high concentrations of alcohol in the stomach may cause delayed gastric emptying (134-137); the latter factor is necessary to be considered in some cases of poisoning. Alcohol use is commonly reported as a factor in overdoses involving prescription drugs, implicated in fatal outcomes (138), and is associated with worse outcomes in other types of poisoning (139). The presence of alcohol, especially at high levels, adversely interacts with drugs present in the body altering both their pharmacokinetics and pharmacodynamics (140). In particular, alcohol exacerbates sedating effects of other ingested drugs which likely leads to a lower Glasgow coma scale score. Alcohol intoxication increases the risk for misadventure with venomous animals (e.g. inappropriate handling). It also increases the risk for envenomation after a bite, due to alcohol having vasodilatory effects (81,82), as well as the patient not being able to properly apply first aid. However, this scenario is apparently not a common finding within survivors of snakebite (141).

The role of alcohol in mood disorders

Chronic heavy consumption of alcohol, particularly in susceptible individuals (e.g. patients with past history of mood disorder) can lead to the development of depressive illness either by enhancement of an underlying mood disorder (e.g. chronic dysthymia) and/or inducing a de novo mood disorder i.e. alcohol induced mood disorder (22,142). It is important to recognize this latter condition because the first line treatment is to assist the patient to stop drinking and sometimes this might require referring to an alcohol detoxification program. There is a high prevalence of comorbid mental health problems in patients with AUDs (58-60) and a strong association between bipolar mood disorder and AUD (62). Furthermore, in patients with mental illness, there is also a higher prevalence of substance use disorders in general particularly tobacco (and cannabis) smoking and AUD (58,60). Therefore, it is important to recognize that heavy alcohol use can both induce a mood disorder and/or secondarily exacerbate an underlying depressive condition because suicide remains one of the commonest causes of death in chronic alcoholics (143). Hence, it is imperative to diagnose and treat serious mood disorders in alcoholics as this action could be life-saving. In some cases, for patients with more severe AUDs (e.g. with physiological dependence) and depression, it can be difficult to engage them ideally in abstinence orientated treatments. While there may be some benefit in providing antidepressant therapy along with strategies to reduce drinking. However, maintaining treatment adherence will be challenging; and thus family and other supports are crucial (144).

Pharmacotherapy for alcohol use disorders

For the majority of AUDs especially those within the mild to moderate severity spectrum, pharmacotherapy has little if any significant role to play. Some research has suggested a limited role for the opioid antagonists such as nalmefene and naltrexone in the management of episodic, binge drinking problems (145,146); however, these agents

are generally indicated for more severe AUDs e.g. in alcohol dependence or chronic alcoholism (145-147). These agents are contraindicated in any patient taking opioids or with documented hypersensitivity to such. Broadly, the opioid receptor antagonists appear to act by reducing endogenous opioid facilitation of dopamine release into the nucleus accumbens, which signals reward (148,149). Numerous studies have shown that a significant proportion of alcoholics treated with opioid antagonists (commenced following alcohol detoxification) experience longer periods of abstinence before relapse, drink less during treatment and experience less craving or compulsion to drink (145-147,150). Acamprosate (N-acetyl-homotaurine) appears to antagonize glutamatergic-NMDA (N-methyl-D-glutamate), GABA_A (gamma aminobutyric acid) and mGluR5 (metabotropic glutamate) receptors, all of which have reported activity in relation to the brain's neuro-adaptive response to chronic alcohol intake (150,151). However, the mechanism of action of this drug is not completely understood and some recent reports (animal studies) suggest that the mechanism of action might be related to the calcium formulated with acamprosate (152-154). Similar to the opioid antagonists, acamprosate can attenuate craving. In this sense, it contributes to reduction in alcohol consumption. In addition, based on laboratory and animal studies, it has been shown that acamprosate possess neuro-protective actions, but this effect has not yet been well supported in research (155,156). Baclofen has limited evidence for efficacy in relapse prevention in selected alcoholics (157), while there are concerns about its safety in others (158).

Disulfiram has remained an effective treatment but for a limited population of alcohol dependent patients, probably because many patients are unwilling to take the drug for fear of the adverse consequences if they mistakenly drink and also because some patients wish to reduce but not stop drinking altogether (159,160). Treatment with this drug leads to psychological changes that inhibit drinking (i.e. fear of experiencing the ethanol-disulfiram reaction). Hence, it can be said that disulfiram does not mediate a direct pharmacological efficacy but rather an "indirect" efficacy related to behavioral consequences (159,160). Disulfiram acts by forming an irreversible, covalent bond with the acetaldehyde dehydrogenase enzyme and if a sufficient dose of disulfiram is taken, virtually all of the available acetaldehyde dehydrogenase will be rendered inactive (159,160). However, many prescribers are unaware of the variation in dose-response to disulfiram and instead prescribe a "standard dose" (e.g. 200 mg effervescent tablet daily) only to find that patients are still able to drink, because an insufficient amount of acetaldehyde dehydrogenase is blocked (159,160). If a disulfiram-treated patient exposes to any kind of alcohol including colognes and some commercial alcohol-containing mouthwashes, because the normal pathway of alcohol metabolism is blocked, acetaldehyde accumulates leading to flushing with headache, nausea and vomiting, hypertension and palpitations; and the latter poses additional risk to patients with cardiac disease

(159-163). This reaction can be severe in some patients and the stress (hyper-adrenergic state) evoked by such a reaction has been associated with other adverse outcomes including myocardial ischemia and infarction which has led to the drug contraindication in patients with significant heart disease (164,165). Disulfiram overdose has potential to mediate serious toxicity and initial decontamination is essential and subsequently close monitoring for adverse sequelae (166,167). Overdose with naltrexone appears non-serious and responds to supportive care (168). There is little data on nalmefene or acamprosate overdose; however, it seems likely these substances have low toxicity in overdose.

Although benzodiazepines are used for the treatment of acute alcohol withdrawal (169), they are not recommended for chronic AUD management (63,87-90). They are generally indicated for short-term use in the management of acute alcohol withdrawal (63,87-90). There are a number of other medications such as gamma amino-butyric acid and some anticonvulsants which have been considered by some physicians to be useful for patients who are refractory to the aforementioned pharmacotherapies. However, their evidence-base is deficient according to a number of reviews (149,170,171). It is important to note that pharmacotherapy for AUDs requires particular attention to adherence, as discontinuation is commonly followed by relapse (172). Of further importance to note is the observation that AUDs can be associated with an increased risk for adverse drug reactions in any pharmacotherapy setting (173).

CONCLUSION

AUDs are prevalent medical problems especially in countries where total ban on alcohol use is not imposed, having a spectrum of severity which most of them are less serious and self-limiting in nature. Nevertheless, when considering the population of patients attending EDs (and toxicology services), patients with more severe AUDs are "over-represented" and thus appear to be more common. Patients with severe AUDs are likely to have significant physical and mental co-morbidities and in particular, disorders of cognition which can pose additional management challenges. While patients presenting with alcohol poisoning are generally easy to identify, sometimes AUDs can be difficult to recognize, particularly when alcohol use may have played a contributing role in injuries and other types of poisoning, the conditions that require much of the physician's focus. Therefore, screening interventions are recommended to facilitate the diagnosis particularly when time and circumstances are appropriate. Whenever possible, screening is best delivered in conjunction with brief interventions having evidence for efficacy in reducing alcohol consumption and related harms. Severe AUDs are more likely associated with the risk for alcohol withdrawal reactions and such are exacerbated in the context of acute medical, surgical and psychiatric illnesses. Long term, severe AUDs carry high mortality risk and are recommended for specialized care.

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