South African Addiction Medicine Society Guidelines for the pharmacological management of Alcohol Use Disorder.

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"O thou invisible spirit of wine, if thou hast no name to be known by, let us call thee devil"
Shakespeare's Othello (Act 2 Scene 2)

Introduction

Alcohol use is as old as mankind and alcohol has been used as a socially acceptable psychoactive drug for millennia. The harm associated with alcohol misuse and alcohol use disorders is significant and is experienced in all spheres of our society.

The disease burden attributable to alcohol consumption is significant and represents a substantial health, social and economic burden worldwide. It is an international priority area [1]. Globally, harmful use of alcohol is estimated to result in 3,3 million deaths each year, which is 5.9% of all deaths and 5.1% of the global burden of disease [2]. It is estimated that 320 000 young people between the age of 15 and 29 die annually from alcohol related causes, resulting in 9% of all deaths in that age group [3].

Incidence and Prevalence in South Africa

The South African Stress and Health Survey study, a representative household study that was done between 2002 and 2004 and included 4351 individuals using the WHO composite international diagnostic interview, found that 11,4% individuals met criteria for alcohol abuse and 2,6% for alcohol dependence. [4]

WHO 2011 Global status report on Alcohol and Health echoes this concern. According to this report, the per capita alcohol consumption in South Africa is above the world and region average (9,5l/year); South Africa has among the highest abstention rates in the world (72.9%) and the prevalence of heavy drinking episodes or "binges", is above the world and regional average (45,4%), placing South Africans amongst the riskiest drinkers in the world. In fact, South Africa rates among the top 5 risky drinking countries in the world with a WHO "Pattern of Drinking Score" of 4 out of a potential 5. The higher this score, the larger the alcohol attributable burden of disease for a country.[2]

Schneider et.al. estimated the deaths in South Africa due to alcohol to be at 7,1% (6.6-7.5%) and the years lost due to disability and early death in South Africa due to alcohol at 7% (6.6-7.4%)[5].

The South African Community Epidemiology Network on Drug Use, SACENDU, an alcohol and drug surveillance system operational in 9 provinces in South Africa, confirms that alcohol is the most common primary substance of abuse amongst patients seen at specialist treatment centres across all of their research sites [6]. Due to the significant prevalence, a concrete understanding amongst the medical community regarding a rational approach to the complete medical management of these patients is imperative.

Alcohol Use Disorder – Definition and Diagnostic criteria

The ICD 10 definition is as follows:

"A cluster of behavioural, cognitive and physiological phenomena that develop after repeated alcohol use and that typically include a strong desire to consume, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to alcohol use than to other activities and obligations, increased tolerance and sometimes a physical withdrawal state."[7]

The DSM V criteria involve having a minimum of 2 described manifestations in a 12 month period that are associated with a pattern of alcohol use that has led to significant dysfunction. These

manifestations include tolerance, craving, withdrawal, loss of control, compulsive use and negative consequences.[8]

Neurobiology

For the purposes of this guideline, a brief description of the neurobiological components of alcohol use disorder is necessary to improve the understanding of described treatment options.

Alcohol has re-enforcing properties leading to repeated use, and the core neural pathway believed to be the basis of this re-enforcement is the mesolimbic-dopaminergic pathway from the ventral tegmental area to the nucleus accumbens of the ventral striatum. This pathway is occasionally referred to as the Reward Circuit [9-13]. The main pathways that are thought to be involved include:

1) Dopamine system [9,10]
2) Opioid system [9-11]
3) Gamma-Aminobutyric Acid (GABA) system [9,10]
4) Glutamate system [9,10]

<u>Reward systems:</u>

A) Dopamine system

Dopamine is a neurotransmitter in the mesolimbic system and affects incentive motivation. Alcohol ingestion and anticipation that alcohol will be available, produce dopamine release in the nucleus accumbens [13]. Alcohol withdrawal produces a reduction in dopamine function, which may contribute to withdrawal symptoms and relapse [9,13].

B) Opioid system

Endogenous opioids, that resemble morphine, are naturally produced in the body and interact with 3 subtypes of receptors – mu, delta and kappa opioid receptors [9,13]. Positive alcohol re-enforcement may be mediated by the direct effect of alcohol on the mu opioid receptors or by the release of endogenous opioids[12]. This hypothesis is supported by demonstrating that opioid antagonists suppress alcohol drinking by blocking the euphoric effect and therefore increasing abstinence [12,13]. Complete knock-out of mu-receptors in mice, blocks alcohol self administration in these mice [9,14]. Therefore, opioid receptor blockers are particularly effective in reducing heavy drinking [9,11,12].

C) GABA system

GABA is the major inhibitory neurotransmitter in the brain [9]. Two receptor subtypes are described – $GABA_A$ and $GABA_B$ [9]. Alcohol causes an increase in GABA activity in the brain via 2 mechanisms; pre-synaptic effects include an increase in GABA release and post-synaptic effects include an increase in $GABA_A$ receptor activity [9,12]. These concepts are further supported by the effect of $GABA_A$ antagonists and $GABA_B$ agonists on suppression of alcohol drinking. Chronic use of alcohol causes a decreased sensitivity of $GABA_A$ receptors to both alcohol and GABA [9]. This helps to explain the development of alcohol tolerance [15]. This down regulation of the GABA inhibitory system, results in hyper-excitability during withdrawal, thereby providing an explanation for the anxiety, tremor, disorientation and hallucinations associated with alcohol withdrawal [15].

D) Glutamate system

Glutamate is the major excitatory neurotransmitter in the brain [9,13]. It exerts its effect via several receptor subtypes including N-methyl-D-aspartate (NMDA) receptor [9,13]. Alcohol inhibits glutamate activity and repeated alcohol consumption ultimately results in dysregulation of this receptor system, which may partially explain the development of alcohol cravings [9,16]. Medication targeting this system can be used to reduce the risk of relapse.

Other neurobiological pathways of interest in alcohol use disorder, are the cannabanoid and neuropeptide-y receptors. These may be targets for future treatment options in alcohol dependence [11,12].

During alcohol withdrawal, the key changes involve reduced GABA levels, reduced GABA receptor sensitivity and activation of the glutamate system (NMDA receptors), thereby resulting in nervous system 'hyperexcitability' (Sympathetic hyper-arousal).[9-12,15] Treatment options are thus based on targeting GABA pathways. Benzodiazepines are the primary treatment option for alcohol withdrawal and act by enhancing inhibitory GABA action [9,15].

Screening and brief interventions:

Risky drinking is common and often goes undetected. Multiple studies have confirmed the effectiveness and cost-effectiveness of screening, brief interventions and referral to treatment (SBIRT) within routine health care and in various other settings. [17-21]

Persons who screen positive for at-risk drinking, need to be reviewed for the presence of an alcohol use disorder.

Persons who drink at risky levels should receive a brief intervention and those who meet criteria for an alcohol use disorder, should be referred for specialized care. A brief intervention consists of the provision of personally relevant feedback using the information obtained during screening, where feedback is provided about the level of risk associated with the person's substance use in an objective manner. [17-22]

Multiple screening tools for alcohol use disorders are available, e.g. CAGE, TWEAK, MAST and AUDIT, etc. Patients may also be asked about heavy drinking days in the last year (men > 4 drinks per day and women > 3 drinks per day) as well as average number of drinks per week (men > 14 drinks per week; women > 7 drinks/ week). [21]

The WHO's AUDIT is a 10-item scale, sensitive for identifying current and low level hazardous drinking in both adolescents and adults. It is less sensitive in the elderly. It is available in the public domain. [21,22]

TWEAK is an "acronym for Tolerance, Worry about drinking, Eye-opener (morning drinking), Amnesia (blackouts), and Cut down on drinking (K/C)". TWEAK is a useful screening tool; it is quick to administer (it takes less than 2 minutes to administer) and was designed to pick up low level alcohol use in pregnancy, but was also found to be sensitive in males and is comparable to AUDIT. [23,24]

"The TWEAK is scored on a 7-point scale. On the tolerance question, 2 points are given if a woman reports that she can consume more than five drinks without falling asleep or passing out. A positive response to the worry question yields 2 points, and positive responses to the last three questions yield 1 point each. A woman who has a total score of 2 or more points is likely to be an at-risk drinker."[25]

**Appendix A - AUDIT Screening questionnaire , **Appendix B – TWEAK Screening questionnaire

Assessment

Assessment of a patient with an alcohol use disorder involves comprehensive history taking and examination. A detailed physical and mental health assessment forms an important part of this assessment, as there is significant risk of medical and mental health co-morbidity.

Evaluate the extent of alcohol withdrawal as well as the risk of withdrawal complications (seizures, delirium tremens). Monitoring and re-assessment of the withdrawal features will guide the treatment provider regarding further management, interventions and possible referral if required. Be aware that other clinical conditions can mimic some features of alcohol withdrawal. Also, be mindful of the possible medical complications associated with heavy alcohol use. These may include gastritis, gastro-oesophageal reflux, pancreatitis with secondary diabetes, liver dysfunction, cardiomyopathy, lung pathology secondary to aspiration, renal dysfunction, musculoskeletal and head injury, plasma electrolyte disturbance, folate deficiency and thiamine deficiency with secondary Wernicke's encephalopathy.[15]

Special investigations are determined by clinical need. A specific marker of alcohol use is the carbohydrate deficient transferrin (CDT), an enzyme with a half-life of about 15 days. Non-specific markers of alcohol use include an increased Mean Cell Volume or Gamma Glutamyl Transferase[26,27]. Blood or breath alcohol levels may be helpful.

Breathalysing patients as part of the assessment is useful, as breath alcohol levels can provide a quick objective measure of current blood alcohol levels.

A urine drug screen is strongly recommended, to rule out any other substance used (including illicit substances) which the patient might not think is a problem. Concomitant use of "downer" drugs, like benzodiazepines and opioids complicates detoxification and needs to be carefully addressed in the treatment plan.

Alcohol withdrawal

Alcohol withdrawal syndrome is a cluster of symptoms that occurs in alcohol dependent individuals after cessation or reduction in alcohol use. This can vary from mild to serious, and the onset of symptoms typically occurs a few hours after the last alcohol intake. The most common manifestations are tremor, restlessness, insomnia, sweating, tachycardia, nausea, vomiting, agitation, hallucinations and seizures. Delirium tremens (DT's) occurs in a small number of patients.[8]

Table 1 (ref - Alcohol Withdrawal Syndrome. M Bayard, J Mcintyre, K R. Hill, J Woodside.Am Fam Physician. 2004 Mar 15;69(6):1443-1450.)[28]

Time of appearance of symptoms of alcohol withdrawal after last alcohol use.

Symptoms	Time since last alcohol use
Insomnia, tremor, nausea, anxiety, sweating, headache, palpitations	6 to 12 hours
Visual, auditory or tactile hallucinations	12 to 24 hours
Withdrawal seizures	24 to 48 hours
Delirium tremens – hallucinations, confusion, agitation, tachycardia, raised blood pressure, sweating, tremor	48 to 72 hours

The above times are estimates and each patient needs to be monitored for withdrawal features using CIWA-Ar scale.

Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)

The revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scale can be used to quantify the severity of the alcohol withdrawal syndrome, and to monitor and medicate patients. CIWA-Ar is a 10-item assessment tool which can be done quickly in the clinical environment. [15,29,30]

A score of :

- 8 or less - mild alcohol withdrawal
- 9 to 15 – moderate withdrawal
- Greater than 15 – severe withdrawal, with an increased risk of seizures and delirium tremens.

Certain medical and mental health conditions may mimic alcohol withdrawal symptoms and signs and some medication may blunt these symptoms and signs.[28]

** Appendix - C

Criteria for In-patient treatment: [31,32,33]

- Moderate to severe alcohol withdrawal features
- A previous history of withdrawal seizures or epilepsy
- A previous history of delirium tremens
- History of continuous heavy drinking with high levels of tolerance
- Previous failed out-patient detoxification or numerous detoxification attempts
- Significant co-morbid medical conditions, which may become worse during the alcohol withdrawal syndrome
- Clinically unstable
- Not able to tolerate oral medication
- Significant psychiatric comorbidity (e.g. psychotic, suicidal, cognitive impairment)
- Poor support structure
- Pregnancy
- Younger than 12 years or elderly
- Significant poly-drug use of CNS depressants

Guidelines for outpatient / community withdrawal management :[31,32,34]

- Mild to moderate alcohol withdrawal syndrome
- Patients should have someone at home who is able to monitor and supervise the withdrawal process
- The treatment plan should be discussed with both the patient and the person providing supervision; it is helpful to write out the regime and keep a copy in the notes.
- Arrange for the patient to be seen daily where appropriate, especially initially
- If the patient resumes drinking, the regime needs to be stopped
- Ensure that the patient and carer has contact details so that they can contact the health facility if there are any problems
- Referral to an out-patient psychosocial support program

General Care during inpatient detoxification:

- Monitor vital signs
- Correct fluid, electrolyte and nutritional deficiencies
- Intravenous fluids if necessary
- Thiamine replacement should be considered in all clients presenting with a history of alcohol abuse.[32,35]
- Routine supplementation with magnesium has not been shown to improve withdrawal symptoms[36]. However if the patient is shown to be hypomagnesemic, magnesium replacement should be included in the management.
- Psychological support is important

- Continuous monitoring of vital signs, withdrawal features including CIWA-Ar

Pharmacological management of alcohol withdrawal syndrome

Benzodiazepines:

Benzodiazepines are first line treatment for the management of the alcohol withdrawal syndrome, and are shown to reduce the severity of withdrawal including reducing the risk of seizures, delirium tremens and death[37]. Different benzodiazepines have been shown to be equally effective in the management of alcohol withdrawal.

The choice of benzodiazepine is determined by the half-life[38]. Shorter acting benzodiazepines (e.g. Oxazepam, Lorazepam), may result in greater discomfort as the withdrawal symptoms tend to recur when the serum benzodiazepine levels decline. The shorter acting benzodiazepines work better in fixed dose regimens and have the advantage of being safer in patients that have significant liver dysfunction. Longer acting benzodiazepines (e.g. Diazepam, Chlordiazepoxide, Clonazepam) may be associated with a 'smoother' withdrawal and less breakthrough withdrawal features. These may also be associated with better seizure control and effectiveness in delirium tremens. However, these agents may lead to excessive accumulation, with drowsiness in patients with hepatic dysfunction and the elderly.[35]

The duration of pharmacological management for alcohol withdrawal should be individualised and on average, lasts about 7 days.[35]

Benzodiazepines can be used as a fixed dose regimen, a symptom triggered regimen or using a front-loading regimen.[32,33]

A fixed dose benzodiazepine regimen implies that a predetermined fixed dose with fixed intervals is used and additional medication may be used to "top-up" according to clinical need.[32]

When symptom triggered regimes are used, benzodiazepine doses are determined by the presence of objective withdrawal features. Although the use of this regimen has shown to use less medication, it requires inpatient care and adequately trained staff. The CIWA-Ar scale can be used as an objective assessment of the withdrawal features when using a symptom triggered withdrawal regime. It is suggested that if this approach is used, that monitoring takes place 6 hourly for mild withdrawal features, 4 hourly for moderate withdrawal features and 2 hourly or less for severe withdrawal features. Clinical observation should always include vital signs (Blood pressure, pulse rate, respiratory rate).[32,33,39]

Front-loading detoxification implies that high doses of long-acting benzodiazepines are administered early in the withdrawal phase and the long duration of action then results in a "self-tapering" effect. This is usually followed by a symptom triggered dosing method.[32]

Examples of detoxification regimes:

1) **Fixed dose diazepam regime:**

Mild alcohol withdrawal features (adjust according to clinical response: reduce dose if patient appears sedated; increase dose if inadequate symptom control or consult an expert)

- Day 1 – 5 to 10mg 6 hourly
- Day 2 – 5 to 10mg 8 hourly

- Day 3 – 5 to 10mg 12 hourly
- Day 4 – 10mg at night
- Day 5 – 5mg at night
- Day 6 – stop

2) Symptom triggered diazepam dosing:

Mild to moderate withdrawal features: 5 to 10mg diazepam

Moderate to Severe withdrawal features : 10 to 20mg diazepam

3) Loading dose diazepam therapy: (*ICU/High Care environment)

20mg Diazepam every 2 hours until 60mg to 80mg or the patient has slight drowsiness but is arousable. Alcohol withdrawal is monitored 2 hourly using the CIWA-Ar and if the score is less than 8 than the dose of diazepam is omitted.[32,40,41]

4) Fixed dose oxazepam regime:

Mild alcohol withdrawal features: (adjust according to clinical response: reduce dose if patient appears sedated; increase dose if inadequate symptom control or consult an expert)

- Day 1 – 10mg 6 hourly
- Day 2 – 10mg 8 hourly
- Day 3 – 10mg 12 hourly
- Day 4 – 10mg at night
- Day 5 – stop

Moderate to severe alcohol withdrawal features: (adjust according to clinical response: reduce dose if patient appears sedated; increase dose if inadequate symptom control or consult an expert)

- Day 1 to 3 – 20mg 6 hourly
- Day 4 onwards – reduce by 10mg per day

PLEASE NOTE, THAT THE ABOVE REGIMES ARE MERELY EXAMPLES AND THAT THE DOSES OF BENZODIAZEPINES SHOULD BE COMMENCED AND ADJUSTED ACCORDING TO INDIVIDUAL PATIENT CLINICAL REQUIREMENTS AND CLINICAL RESPONSE.

It is important to note that benzodiazepines may cause sedation and respiratory suppression in overdose. Patients therefore require supervision and monitoring during detoxification. Extreme caution is advised with the concomitant use of other central nervous system depressants as these drugs may have a cumulative effect. Withdrawal from more than one CNS depressant requires expert care.

Other medication that can be used for alcohol withdrawal features:

a) Gabapentin:
   Gabapentin is used as adjunct therapy for partial seizures and monotherapy for non-epileptic conditions such as management of certain pain related conditions, movement disorders, bipolar disorder and social phobia[42]. Some recent studies have shown positive results in the management of alcohol withdrawal features[43-48].
b) Carbamazepine:

Carbamazepine has shown to be effective in the treatment of the alcohol withdrawal syndrome[47,48].

c) Valproic acid[34,49] and Divelproax[50]:
May be effective but are limited by side effects.

Importantly, if a patient is on a regular anticonvulsant prescription, these need to be continued and levels monitored. If these are stopped the risk of withdrawal seizures are greater[32].Other medication like alpha-adrenergic agonists (Clonidine), B-blockers and Calcium Channel Blockers should not be considered as monotherapy options for the management of alcohol withdrawal syndrome[37].

Thiamine Replacement

Thiamine (Vitamin B1) is necessary for several biochemical pathways in the brain, such as intermediate carbohydrate metabolism (for energy production), lipid metabolism (for production and maintenance of the myelin sheath) and production of amino-acids and glucose derived neurotransmitters.[51]

Those who misuse alcohol are at risk of thiamine deficiency due to associated factors such as self-neglect, malnutrition, low content of vitamins and minerals in alcoholic beverages, decreased transport of thiamine across intestinal mucosa, low capacity of the liver to store the vitamins and the impaired conversion of thiamine to the active compound thiamine pyrophosphate.[51]

Thiamine deficiency may lead to Wernicke's encephalopathy (WE), an acute neuropsychiatric syndrome, which is characterised by nystagmus, opthalmoplegia, mental state changes and ataxia of the gait or limbs. This triad is however only seen in 16% of patients.[51]

WE is associated with a 17% mortality rate[52]. Eighty percent of patients with WE who survive will develop Korsakoff's syndrome, a disorder characterized by severe memory deficits.[52]

Operational criteria for WE (Caine et al 1997 [53]) requires 2 of the following:

1) Dietary deficiencies
2) Oculomotor abnormalities (opthalmoplegia, nystagmus, gaze palsy)
3) Cerebellar dysfunction (ataxic gait, ataxia of the limbs)
4) Either an altered mental state or mild memory impairment

It has also been suggested that a presumptive diagnosis of WE should be made in any patient undergoing alcohol detoxification and experiences any one of the following: ataxia, hypothermia, hypotension, confusion, opthalmoplegia/nystagmus, memory impairment and a change in level of consciousness.[54]

Management:

WE is a medical emergency that requires either intravenous or intramuscular thiamine to ensure adequate absorption. Parenteral thiamine administration is generally safe[51] but if provided, facilities for treating anaphylaxis should be available.

1) If WE is suspected[35]:

• Thiamine Hydrochloride 500mg dissolved in 100ml of normal saline given by infusion over 30 min, three times a day for 2-3 days.

• If an effective response is observed, continue with thiamine 250mg either intravenously or intramuscularly for 3-5 days or until clinical improvement has ceased.

2) Patients at high risk of WE[35]:

• It is generally advised that patients undergoing inpatient detoxification and at risk for WE should be given parenteral thiamine, using 250mg IMI or IVI for 3-5 days and then followed by oral thiamine.

3) Healthy uncomplicated heavy drinkers/alcohol–dependent[35]:

• Should continue with thiamine 300mg during detoxification and during periods of continued alcohol use.

Delirium Tremens

The impact of complications of alcohol withdrawal on outcomes can be significant. The incidence of alcohol withdrawal seizures(AWS) is 4 – 6% and for delirium tremens(DT) 4 – 15% [55]. Delirium Tremens is the harshest consequence of alcohol withdrawal syndrome. The patient presents with a sudden alteration of awareness, attention and cognition (sometimes with hallucinations) and can fluctuate significantly [8,56]. Due to the significant associated morbidity and mortality, as well as the burden that these can create on medical services, strategies to predict risk for for AWS and DT are thus important for appropriate and prompt management [55,56].

Some predictors of risk have been proposed:

- Previous history of withdrawal seizures[55] - Patients with withdrawal seizures had a 3 times greater risk of delirium tremens compared to individuals who did not have withdrawal seizures[55]
- Previous alcohol detoxifications - the 'kindling' concept has been described with alcohol withdrawal – the severity of the withdrawal features worsen after repeated detoxification and relapses. This may also be the case in binge pattern drinking[55,57,58]
- Previous delirium tremens
- Structural brain lesions[55]
- Low platelets[55,56]
- Low potassium[55]
- High blood homocysteine levels[56]
- CIWA-Ar scores above 15[59]
- Elderly[59]
- Concurrent abuse of other CNS depressants (including illicit use) [59]

Treatment of patients presenting with alcohol withdrawal seizures or delirium tremens should ideally be managed in a high care or intensive care setting. General care, thiamine replacement and monitoring should be implemented as described above, but much more frequently. Pharmacotherapy should primarily be the use of benzodiazepines (e.g. Diazepam). Administered intravenously, the benzodiazepines should be given at a rate that reduces the alcohol withdrawal features and imparts slight drowsiness but the patient should still be arousable. Appropriate doses of benzodiazepines and continuous monitoring should be implemented concurrently until the delirium improves. Adjunct medication in the form of antipsychotics can be used to treat agitation and hallucinations which are difficult to control with benzodiazepines alone.[32,59]. However, it is important to note that antipsychotics can alter QT intervals which can potentially aggravate seizure threshold[59].

We refer the interested reader to M Shuckit, who in his article, "Recognition and management of withdrawal delirium (Delirium Tremens)", provides some examples of regimens of diazepam and lorazepam that can be used in the management of delirium tremens[59].

Rarely, patients can be resistant to the management strategies described above and some authors have described the possibility of using propofol in these intubated patients [59,60].

Psychosocial modalities

Evidence has highlighted that medication and detoxification alone does not improve outcomes. Combination with psychosocial interventions has shown to be effective regarding positive outcomes.This is the 'umbrella' of holistic, multidisciplinary care.These interventions can include individual therapy, group therapy including 'self-help' groups (Alcoholics Anonymous), social skills training, family and caregiver support and education and relapse prevention. Motivational Interviewing, brief intervention, cognitive behavioural therapy and relapse prevention therapy are some forms of individual therapy. Group therapy is included as part of a structured program and serves to address stressors, coping mechanisms, explore positive and negative thoughts around alcohol use. All interventions should be individualized according to need.[61,62,63]

Relapse Prevention

Alcohol use disorder is a chronic condition and therefore maintaining sobriety is a continuous process. This section will deal with some of the pharmacological strategies available in South Africa. It is important to note that these strategies are not 'stand-alone' and have to be part of a comprehensive relapse prevention model, which includes an individualised psychosocial treatment plan[35].

<u>Disulfiram (Antabuse)</u>

Disulfiram acts as a psychological deterrent for alcohol use in motivated clients who struggle with sobriety.[32,64]

Acetaldehyde is generated in the liver during the metabolic breakdown of alcohol. Normally, the enzyme aldehyde dehydrogenase is responsible for converting acetaldehyde to acetate. Disulfiram is an inhibitor of aldehyde dehydrogenase and when alcohol is consumed while taking disulfiram the build-up of acetaldehyde leads to an aversive and potentially dangerous reaction, which includes tachycardia, flushing, nausea and vomiting, headaches, seizures and in severe cases death. The use of disulfiram thus requires informed consent from the patient.[32,35,64]

Disulfiram has shown to have positive results when daily consumption is supervised[65] and as an adjunct to supportive and psychotherapeutic treatment[32,35,64]. The length of time for treatment is variable, and progress of the patient (including medical, psychological and social well-being) would usually dictate this. Side-effects can include headache, drowsiness, dermatitis, metallic aftertaste, worsening of liver enzymes and psychiatric disturbances[32,66,67]. It is recommended that liver function tests are done prior to commencement of treatment, and then at 1 month, 3months and 6 months and 3-monthly after that. Use disulfiram with caution if the patient has heart problems, history of psychosis, epilepsy, diabetes, liver or kidney disease[67]. Avoid in pregnancy and during breastfeeding[67]. Also note possible drug interactions may occur with certain psychiatric medications, tuberculosis treatments and metronidazole[67].

Disulfiram should only be commenced 12 to 24 hours after the last alcohol intake and patients should also be advised to wait at least 7 days after stopping the medication, should they decide to consume alcohol again. Patients should be advised to avoid alcohol-containing medication,

mouthwash and food products as well as "hidden" sources of alcohol, like cologne, aftershave, perfumes, lotions and occasionally vinegar containing products[64,66].

The dosage range is 200-400mg/day.[32]

"**Disulfiram Black-Box Warning - Disulfiram should never be administered to a patient who is in a state of alcohol intoxication or without the patient's full knowledge. The physician should instruct relatives accordingly.**"[67]

An important aspect of Disulfiram prescribing is , therefore, obtaining signed consent from the patient after the patient is fully counseled.

Acamprosate

Acamprosate is thought to act by normalizing the NMDA mediated glutaminergic neurotransmission, by reducing NMDA receptor transmission and enhancing GABA receptor transmission. It adds a modest effect in improving relapse to alcohol by reducing cravings for alcohol, thereby maintaining abstinence superior to placebo when used in conjunction with a psychosocial treatment intervention.[35,64]

Acamprosate seems to be well tolerated with only occasional gastrointestinal side effects. Contraindications include pregnancy or breast-feeding, severe renal (creatinine clearance < 30ml/min) and hepatic dysfunction[68]. It can be started as soon as the patient is detoxified from the alcohol or 5 days after last drink. The dosage is commenced at 666mg three times daily for adults>60kg. In adults < 60kg commence at 666mg mane, 333mg midday and 333mg at 6pm[69]. The duration of treatment can be up to a year, and depends on the progress of the patient with regards to achieving goals of maintaining abstinence, decreased cravings, stabilised social & support structure and a safe and realistic continuity plan within recovery[68].

Acamprosate can be stopped if the patient is non-compliant on the medication. However, drinking alcohol is not necessarily a reason to stop Acamprosate and requires a review of the recovery plan, establishing boundaries and continued Acamprosate use, while monitoring the patient continuously.

Naltrexone:

Opioid antagonists, like Naltrexone, decrease the reinforcing effects of alcohol, which can result in a reduction in harmful drinking[35,64]. Although Naltrexone is licensed in some countries for the treatment of alcohol use disorder (FDA approved Naltrexone for the treatment of alcohol use disorders in 1994[67]); it is currently used off-label for this indication in South Africa.

Naltrexone is available in South Africa and is licensed for use in opioid dependence. Nalmefene is an opioid system modulator with mu and delta receptor antagonistic effects. Evidence shows that Nalmefene leads to reduced drinking and therefore reduced alcohol related harm[70,71]. Nalmefene is not available in South Africa at present.

Naltrexone has been shown to have benefit in alcohol use disorder particularly in achieving outcomes like abstinence, relapse rate, time to first drink, reduction in number of drinking days, reduction in craving and improved GGT.[35,64]

The dose of naltrexone is 50mg daily, taken orally[32,35,64].

Other treatments that show promise:

Emerging evidence is showing promising results for the use of Topirimate[32,48] and Gabapentin[32,72], certain antipsychotics[32,75], Baclofen[32,73,74] (muscle relaxant), sodium oxybate[76] and ondansetron[77] as medication options in relapse prevention.

Aftercare/ Follow-up

Monitoring the patient and continuously assessing relapse risk is an important component of the holistic management, which is often neglected. The following strategies can be implemented as part of aftercare[78]:

- Establishing and maintaining a trusting, supportive relationship with the patient
- Regular follow-up appointments, according to 'needs' of the patient. Monitor pharmacotherapy dosing/effects/side-effects. Review physical and biochemical abnormalities which may have been established during the initial assessment. Monitor markers of chronic alcohol use (as described earlier)
- Address cravings and assist patients with developing coping mechanisms for these
- Advise the patient on general lifestyle modification strategies which will help reduce relapse risk
- Actively monitor for co-morbid mental health and physical conditions. Referral as necessary to specialists (I.e psychiatrist, physician, e.t.c.)
- Incorporate the patients' support structures (family) into the aftercare plan, including providing support (directly or as information) to them
- Encourage continuity in structured psychosocial programs
- Ask the question at each visit. Was the patient able to meet and sustain goals? If not, understand that change is difficult, so support any effort made, relate to drinking problems and address co-existing disorders[79].
- If uncertain or persistent problems – refer the patient to specialist addiction services

Conclusion

Guidelines on alcohol consumption vary from country to country and have also changed over the years. In 2003 the South African Department of Health adopted a set of Food-Based Dietary Guidelines (FBDG), which included a 'comment ' regarding alcohol use – "If you drink alcohol, drink sensibly"[80]. In 2011 the FBDG was reviewed which included addressing the very "confusing" and vague statement regarding alcohol in the 2003 guideline[81]. The current guideline indicates that females should not exceed "1 drink per day" and males should not exceed "2 drinks per day"[81]. Unfortunately, a definition for "1 drink" in terms of quantity was not given. In an attempt to create some guidance in this document, we found that the generally accepted standard unit of alcohol in South Africa is 12g of alcohol.

The World Health Organization (WHO) Guide to Mental Health in Primary Care describes three levels of risk: "responsible," "hazardous" and "harmful".[82]

The WHO guideline, however, is based on 1 unit being equivalent to 8g of ethanol[82]. Therefore, based on the above information, South African recommended drinking limits should be:

(1 unit / 'drink' = 12grams of alcohol)

"Responsible risk", 'low' or 'moderate' use:

- Men - 2 units per day - maximum of 14 units per week spread throughout the week (including 2 alcohol free days per week)
- Women – 1 unit per day and 7 per week.
- Not all in one day (avoid binges)

“Hazardous ” level of consumption:

- Men – 2-5 units per day and 14-35units per week
- Women – 1-3 units per day and 7-21 per week

“Harmful” level of consumption:

- Men - 6 or more units per day, or over 42 units per week
- Women – 4 or more units per day and over 28 units per week

Other suggested safe guidelines for drinking:

- Not during pregnancy
- Never before or during driving, swimming, active sport or use of machinery, electrical equipment, ladders or in other potentially dangerous situations.

Alcohol intake can be considered harmful when it elevates risk for alcohol-related health or social problems or complicates the management of other health/social problems[83].

The Industry Association for Responsible Alcohol Use, on their website, highlight the different quantities of alcohol in each major type of alcoholic beverage:

“A 340ml malt beer (at a typical 5% alcohol by volume) contains 12g of alcohol; a 340ml cider (at a typical 6% alcohol by volume) contains 16g of alcohol: a 25ml tot of brandy, whisky, gin, cane or vodka (at a typical 43% alcohol by volume) contains 11g of alcohol; and a 120ml glass of wine (at a typical 12% alcohol by volume) contains 11g of alcohol”.[84]

Another essential goal of this guideline is to prevent poor clinical practice that is associated with poor outcomes in the management of alcohol use disorders. These include[85]:

- detoxification as a stand alone treatment
- unstructured group therapy
- any of the following as exclusive modalities -: acupuncture, relaxation therapy, didactic group education, biological monitoring of substance use, individual psychodynamic therapy
- confrontation as a principal treatment approach
- discharge from a treatment program in response to relapse

These guidelines have been developed, to maintain the South African Addiction Medicine Society vision of promoting safe, evidence based and ethical treatment of addiction in South Africa. The intention was to also provide a guideline which could be applied diversely in both state and private medical sectors in South Africa and thus aligning itself with part of the National Drug Master Plan 2013-2017[86] vision.

“Lechery, sir, it provokes, and unprovokes; It provokes the desire, but it takes away the performance. Therefore much drink may be said to be an equivocator with lechery: it makes him and it mars him; it sets him on and it takes him off. it persuades him, and disheartens him; makes him stand to, and not stand to; in conclusion, equivocates him in a sleep, and, giving him the lie, leaves him.” - William Shakespeare – Macbeth, Act 2, Scene 3.

Appendix A

AUDIT Screening Questionnaire

The Alcohol Use Disorders Identification Test: Self-Report Version

PATIENT: Because alcohol use can affect your health and can interfere with certain medications and treatments, it is important that we ask some questions about your use of alcohol. Your answers will remain confidential so please be honest.

Place an X in one box that best describes your answer to each question?

Question	0	1	2	3	4	
1. How often do you a drink containing alcohol?	Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week	
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more	
3. How often do you have six or drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
6. How often during the last year have you needed a first drink in the morning to get you going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
9. Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, during the last year	
10. Has a relative, friend, doctor, or other healthcare worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year	

Appendix B:

TWEAK Screening Questionnaire

Question		**Answer**	**Points**
How many drinks does it take before you begin to feel the first effects of alcohol? Or How many drinks does it take before the alcohol makes you fall asleep or pass out? If you never pass out, what is the largest number of drinks that you have?	Tolerance	3 or more drinks 5 or more drinks	2 points
Have your friends or relatives worried about your drinking in the past year?	Worried	Yes	1 point
Do you sometimes take a drink in the morning when you first get up?	Eye-opener	Yes	1 point
Are there times when you drink and afterwards can't remember what you said or did?	Amnesia	Yes	1 point
Do you sometimes feel the need to cut down on your drinking?	K/C Cut down	Yes	1 point

Appendix C

Addiction Research Foundation Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)
Patient _____ Date _____ Time _____
Pulse or heart rate, taken for one minute: _____ Blood pressure: _____/_____

NAUSEA AND VOMITING – Ask "Do you feel sick to your stomach? Have you vomited?" Observation.
0 no nausea and no vomiting
1 mild nausea with no vomiting
2
3
4 intermittent nausea with dry heaves
5
6
7 constant nausea, frequent dry heaves and vomiting

TREMOR – Arms extended and fingers spread apart. Observation.
0 no tremor
1 not visible, but can be felt fingertip to fingertip
2
3
4 moderate, with patient's arm extended
5
6
7 sever, even with arms not extended

PAROXYSMAL SWEATS - Observation
0 no sweat visible
1 barely perceptible sweating, palms moist
2
3
4 beads of sweat obvious on forehead
5
6
7 drenching sweats

TACTILE DISTURBANCES – Ask "Have you any itching, pins and needles sensations, any burning, any numbness or do you feel bugs crawling on or under your skin?" Observation
0 none
1 very mild itching, pins and needles, burning or numbness
2 mild itching, pins and needles, burning or numbness
3 moderate itching, pins and needles, burning or numbness
4 moderately server hallucinations
5 severe hallucinations
6 extremely server hallucinations
7 continuous hallucinations

AUDITORY DISTURBANCES – Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?" Observation
0 not present
1 very mild harshness or ability to frighten
2 mild harshness or ability to frighten
3 moderate harshness or ability to frighten
4 moderately server hallucinations
5 severe hallucinations
6 extremely server hallucinations
7 continuous hallucinations

AUDITORY DISTURBANCES – Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?" Observation
0 not present
1 very mild harshness or ability to frighten
2 mild harshness or ability to frighten
3 moderate harshness or ability to frighten
4 moderately server hallucinations
5 severe hallucinations
6 extremely server hallucinations
7 continuous hallucinations

ANXIETY – Ask "Do you feel nervous?" Observation
0 no anxiety, at ease
1 mildly anxious
2
3
4 moderately anxious, or guarded, so anxiety is inferred
5
6
7 equivalent to acute panic states as seen in server delirium or acute schizophrenic reactions

AGITATION - Observation
0 normal activity
1 somewhat more than normal activity
2
3
4 moderately fidgety and restless
5
6
7 paces back and forth during most of the interview, or constantly thrashes about

VISUAL DISTURBANCE – Ask "Does the light appear to be too bright? Is the colour different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?" Observation
0 not present
1 very mild sensitivity
2 mild sensitivity
3 moderate sensitivity
4 moderately server hallucinations
5 severe hallucinations
6 extremely server hallucinations
7 continuous hallucinations

HEADACHE, FULLNESS IN HEAD – Ask "Does your head feel different? Does it feel like there is a band around your head?" Do not rate dizziness or light-headedness. Otherwise, rate severity.
0 not present
1 very mild
2 mild
3 moderate
4 moderately severe
5 severe
6 very severe
7 extremely severe

ORIENTATION AND CLOUDING OF SENSORIUM – Ask "What day is this? Where are you? Who am I?"
0 oriented and can do serial addictions
1 cannot do serial addictions or is uncertain about date
2 disorientated for date by no more than 2 calendar days
3 disorientated for date by more than 2 calendar days
4 disorientated for place and/or person

Total CIWA-A Score _____
Rater's Initials _____
Maximum Possible Score 67

The Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar) (Sullivan et al. 1989; Foy et al. 1988). This instrument rates 10 withdrawal features, takes only a few minutes to administer, and can be repeated easily when necessary. A total score of 15 or more points indicates that the patient is at increased risk for severe withdrawal effects, such as confusion and seizures.

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