

TREATMENT OF ALCOHOL WITHDRAWAL SYNDROME – A PRACTICAL GUIDE IN GENERAL PRACTICE

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ABSTRACT

Alcohol abuse and associated disorders incidence are increasing, and comorbidities in these patients are quite frequent, so when hospitalized for other conditions, withdrawal syndrome may appear quite often. Managing symptoms in general practice may be challenging.

Keywords: alcohol use disorder (AUD); alcohol withdrawal syndrome; benzodiazepines

Alcohol abuse has a high incidence in nowadays, and when people with this addiction suffer other kind of diseases and are hospitalized, withdrawal symptoms appear quite often.

Managing these symptoms can sometimes be challenging, considering comorbidities and individual factors.

Alcohol dependence is considered an addiction, so a disease which includes four categories of symptoms:

- Craving: an irresistible need to drink
- Loss of control: the inability to limit or to stop the consume
- Physical dependence: emerging of withdrawal symptoms when ingestion is stopped after a period of heavy drinking; these symptoms are nausea, sweating, shakiness, anxiety
- Tolerance: the urge to consume higher quantities of alcohol in order to feel well
- According to DSM-5, alcohol abuse and alcohol dependence are now integrated in a single disorder called alcohol use disorder (AUD) with mild, moderate and severe sub-classifications.

Main changes in diagnostic between DSM-IV and DSM-5 criteria, consist in the fact that in former classification abuse and dependence were distinct: anyone meeting one or more of the abuse criteria (items 1-4) within a 12 month period would

receive the “abuse” diagnosis, whereas someone with three or more dependence criteria (items 5-11) during the same period, would receive a “dependence” diagnosis. In DSM-5 classification, anyone who meets any 2 of 11 criteria during the same period of 12 months would receive a diagnosis of AUD, and very important, this later classification eliminates legal problems as a criterion, as it was met in DSM-IV. Also an important issue is the fact that DSM-5 adds craving as a criteria for AUD, which was not included in DSM-IV.

Comparison Table 1 between DSM-IV and DSM-5.

Epidemiologic data: as we know, in USA, where statistics are very accurate, prevalence of drinking in 2013, was considered as follow: 86.8% of people over 18 years reported that they drank alcohol at some point in their lifetime, 70.7% reported that they drank in the past year and 56.4% reported that they drank in the past month. (1)

Regarding alcohol use disorder in USA for adults (ages 18+): 16.6 million adults ages 18 and older (2) (7.0 percent of this age group) (3) had an AUD in 2013. This includes 10.8 million men (9.4 percent of men in this age group) (3) and 5.8 million women (4.7 percent of women in this age group) (3). About 1.3 million adults received treatment for an AUD at a specialized facility in 2013 (7.8 percent of adults who needed treatment). This

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TABLE 1

<i>In the past year, have you:</i>		
DSM-IV		DSM-5
Found that drinking-or being sick from drinking-often interfered with taking care of your home or family? Or caused job troubles/school problems?	1	Had times when you ended up drinking more, or longer, than you intended?
More than once gotten into situations while after drinking that increased your chances of getting hurt (such as driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)?	2	More than once wanted to cut down or stop drinking, or tried to, but couldn't?
More than once gotten arrested, been held at a police station, or had other legal problems because of your drinking? **this is no longer included in DSM-5**	3	Spent a lot of time drinking? Or being sick or getting over other aftereffects?
Continued to drink even though it was causing trouble with your family or friends?	4	Wanted a drink so badly you couldn't think of anything else? (craving) **this is new item in DSM-5**
Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?	5	Found that drinking, or being sick from drinking, often interferes with taking care of your home or family? Or caused job troubles/school problems?
Found that when the effects of alcohol were wearing off, you had withdrawal symptoms, such as trouble sleeping, shakiness, restlessness, nausea, sweating, a racing heart or a seizure? Or sensed things that were not there?	6	Continued to drink even though it was causing trouble with your family or friends?
Had times when you ended up drinking more or longer than you intended?	7	Given up or cut back on activities that were important or interesting to you, or gave pleasure, in order to drink?
More than once wanted to cut down or stop drinking, or tried to, but couldn't?	8	More than once gotten into situations while or after drinking that increase your chances of getting hurt (such as driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)?
Spent a lot of time drinking? Or being sick or getting over other aftereffects?	9	Continued to drink even though it was making you feel depressed or anxious or adding to another health problem? Or after having had a memory blackout?
Given up or cut back on activities that were important or interesting to you, or gave pleasure, in order to drink?	10	Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?
Continued to drink even though it was making you feel depressed or anxious or adding to another health problem? Or after having had a memory blackout?	11	Found that when the effects of alcohol were wearing off, you had withdrawal symptoms, such as trouble sleeping, shakiness, restlessness, nausea, sweating, a racing heart or a seizure? Or sensed things that were not there?
Any 1 from items 1-4 = ALCOHOL ABUSE Any 3 from items 5-11 = ALCOHOL DEPENDENCE		The presence of at least 2 items indicates ALCOHOL USE DISORDER(AUD): MILD = presence of 2 to 3 symptoms MODERATE = presence of 4 to 5 symptoms SEVERE = presence of 6 or more symptoms

Adapted after National Institute of Alcohol Abuse and Alcoholism NIH Publication no. 13-7999 July 2015

included 904.000 men (8.0 percent of men in need) and 444.000 women (7.3 percent of women who needed treatment). (4)

An important issue of this pathology is appearance of the addiction in younger people, so that in the group of ages 12–17 in 2013 an estimated number of 697.000 adolescents (5) (2.8 percent of this age group) (6) had an AUD. This number includes 385.000 females (5) (3.2 percent of females in this age group) (6) and 311.000 males (5) (2.5 percent of males in this age group) (6). An estimated number of 73.000 adolescents (44.000 males and 29.000 females) received treatment for an alcohol problem in a specialized facility in 2013. (7)

So, the global burden of AUD generated in 2013, 3.3 million deaths, representing a 5.9 percent of all global deaths (7.6 percent for men and 4.0 percent for women) (8)

Nevertheless, alcohol contributes to over 200 diseases and injury-related health conditions, most notably alcohol dependence, liver cirrhosis, cancers, and injuries. (9) In 2013, 5.1 percent of the burden of disease and injury worldwide (139 million disability-adjusted life years) was attributable to alcohol consumption. (8)

It is important to remember that, globally, alcohol misuse is the fifth leading risk factor for premature death and disability and among people between

the ages of 15 and 49, it is the first.(10) Globally, alcohol use disorder is one of the most prevalent mental health disorders and leading causes of sickness and death. In the United States, alcohol use disorders and binge drinking have increased in recent years. Unfortunately, only approximately 20% of adults with lifetime alcohol use disorder ever seek treatment or ask for help.

In 2013, in USA, alcohol-impaired driving fatalities accounted for 10.076 deaths (30.8% of overall driving fatalities). (11)

As we could see from epidemiologic data, impact of alcohol consumption in our days is of real importance, so that, whenever such a person is admitted for other pathologies, the risk of developing withdrawal symptoms is quite important.

Treatment of alcohol withdrawal syndrome is one in stages; knowing guidelines will ease our mission for resolving problems, before escalating symptoms and appearance of somatic complications and delirium. Frequent signs and symptoms in withdrawal syndrome are: anxiety or psychomotor agitation, tremor, craving, autonomic hyperactivity(tachycardia, hypertension, sweating, hypertermia, arrhythmia), insomnia, sensory distortions or hallucinations(transient visual, tactile, auditory), nausea or vomiting, seizures, delirium.

TABLE 2. Step evolution of withdrawal symptoms

Minor symptoms	Alcoholic hallucinosis	Withdrawal seizures (12-48 h)	Delirium tremens (DT) (48-72 h)
Anxiety	Visual	Generalized tonic-clonic convulsions	Agitation
Insomnia	Auditory		Hallucinations
Nausea	Tactile		Disorientation
Headache			Tachycardia
Palpitations			Hypertension
Anorexia			Fever
			Diaphoresis
After alcohol cessation	Usually resolves in 48 hours	May occur as early as 2 hours after cessation	Peak at 5 days, lasts up to 7 days

(Adapted after Amercian Academy of Family Physicians)

Benzodiazepines (BZD) are the primary agents used as substitutes, as they are cross-tolerance medications for alcohol withdrawal. They act as substitute for the GABA-modulating effects of alcohol and are extremely safe and effective. Benzodiazepines can be administered with a fixed-schedule or a symptom-triggered regimen with or without loading. It is well known that efficacy is better with a symptom-triggered schedule than with a fixed

one dosing in patients admitted for detoxification (12) but not necessarily for the treatment of DT. Benzodiazepines have similar efficacies in treating alcohol withdrawal syndrome, though differences may exist between drugs according the route of administration, onset of effects on agitation, elimination half-life, active metabolites, and time of effects. First time, a loading dose is given to achieve minimal sedation, followed by maintenance medication. Doses of medication required to achieve efficacy varies with the severity of withdrawal.

Lorazepam can be administered intravenously, intramuscularly, or orally. It provides a long duration of seizure control because of its slow redistribution and it has decreased risk of sedation among patients with liver impairment because of its short half-life and absence of active metabolites. Dose is 1-4 mg every 5-15 minutes until adequate control of agitation is achieved. As adverse reactions, large and rapid doses of lorazepam may induce cardiovascular toxicity due to diluent (propylene glycol).

Diazepam can be administered intravenously, intramuscularly or orally. Diazepam has high lipid solubility, which determines rapid distribution, so it rapidly controls agitation. However, it has a long duration of action so that prolonged sedation is a risk. Initial dose is 5 mg IV. The drug is repeated at 5-20 mg per dose every 5-15 minutes until control of agitation is reached in a comfortable manner. Afterwards, doses are given as needed to maintain light somnolence.

Total doses of intravenous diazepam should not frequently exceed 100 mg/h or 250 mg in 8 hours. Regarding intravenous lorazepam, total dose should not routinely exceed 20 mg/h or 50 mg in 8 hours.

All short-acting agents have a higher incidence of rebound symptoms: oxazepam and midazolam must be carefully tapered to avoid reappearance of symptoms and seizures.

In cases with no response to massive doses of benzodiazepines, intravenous infusion of propofol or intravenous boluses of barbiturates (phenobarbital and pentobarbital) should be added as second-line GABA modulators (13). This treatment is typically effective as the drugs act on different sets of GABA receptors. Propofol also modulates glutamate (NMDA) receptors.

Neuroleptics are not used as first line therapy because sedative-hypnotics have superior efficacy in reducing duration of alcohol withdrawal syndrome and associated mortality. In a severely agitated patient, neuroleptics such as Haloperidol 5 mg intramuscularly or orally, may be added as an adjunctive therapy and repeated with caution in

30-60 minutes if agitation is not controlled, but with caution, as it is known that haloperidol decreases the seizure threshold as well as prolong the QT interval. As well, we can use Tiapridal, intramuscularly or orally, 100-300 mg/daily.

Several other medications are reported to be helpful to add to benzodiazepines and other GABA modulators – barbiturates (14) and propofol (15) – in the treatment of refractory alcohol-withdrawal syndrome, but they are not recommended as a monotherapy. These include baclofen, (16) haloperidol, carbamazepine, (17) valproic acid, (17) clonidine, (18) and beta-blockers (atenolol). (19)

CONCLUSIONS

Benzodiazepines:

- Diazepam 10-20 mg intramuscularly/orally with repeated doses at 2-4-6 hours (max 100 mg/daily), depending on the severity of symptoms; in case of severe agitation, we can use it in perfusion, 0.5 mg/kgc (12-15 mg/min)
- Clordiazepoxid (Napoton: tablets 10 mg) 50-100 mg with repeated doses at 2-4 hours (max 300 mg/daily)

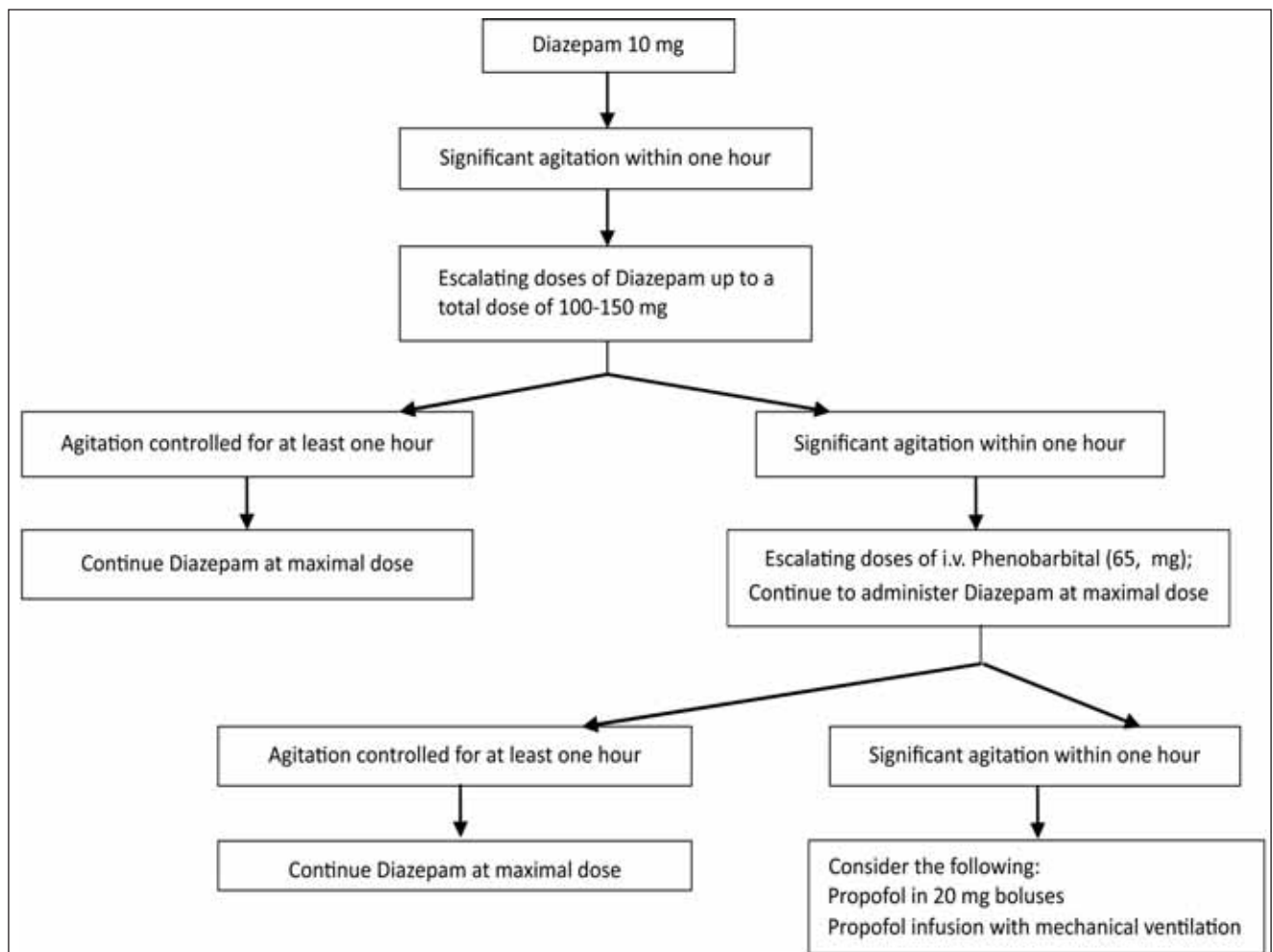
- Lorazepam (Anxiar:tablets 1 mg) 1mg orally, with repeated doses at 4-6 hours (max 4 mg/daily)
- Oxazepam (tablets 10 mg) 15-30 mg (max 30-60 mg/daily)

Total dose of BZD will be decreased with 25% in following days, regarding clinical state, as soon as the second day of therapy and then gradually till the 10th day.

For DT it is wise not to use neuroleptics, as these drugs lower the seizure threshold and can precipitate more complications. Using in correct doses Diazepam/Lorazepam can ease anxious agitation in this phase.

Barbiturate use was abandoned as they may cause extreme sedation because of their remanent action with accumulation risk, so that in nowadays they are used only in extremis cases, when full doses of BZD don't accomplish sedation. We can still use Pheno-barbital but no more than 50-120 mg once, with a repeat dose not earlier than 30 minutes.

Last solution for these patients with extreme agitation is the use of anesthetics like Propofol, in Intensive care units.



Rehydration and rebalancing electrolytes, as well as administering thiamine (100-200 mg/daily) are also very important.

Non-pharmacological measures are as well important:

- patient survey for 48-72 hours in a well but not directly lit room (for lowering anxiety and the possibility of worsening disturbances of perception, as this is the time when DT is considered a major medical and metabolic emergency, and only afterwards a psychiatric one!)
- somatic examinations every 2-4 hours, including temperature, for preventing complications (pulmonary, cardiac, seizures)

N.B. Unfortunately, in Romania, injectable Lorazepam is not registered, so the only benzodiazepine we can administer intravenously in alcohol withdrawal syndrome is Diazepam.

Of course, after resolving withdrawal syndrome and the main reason for admittance in hospital, patient must be advised regarding cessation of alcohol abuse or alcohol dependence, by addressing the underlying disease of addiction. This may be done with psychotherapy and, when necessary, even medication, as relatively brief outpatient interventions can be effective for alcohol abuse, but more intensive therapy may be required for alcohol dependence. Patient may join a 12-step group, such as Alcoholics Anonymous in combination with cognitive-behavioral therapy, and family therapy, as it is well known that presence of an addicted person in the family is a main disturbing factor, impacting every other person.

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