Alcohol withdrawal delirium - diagnosis, course and treatment

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Objective. Delirium tremens represents the most severe complication of alcohol withdrawal syndrome and, in its complications, significantly increases the morbidity and mortality of patients. Alcohol withdrawal delirium is characterized by features of alcohol withdrawal itself (tremor, sweating, hypertension, tachycardia etc.) together with general delirious symptoms such as clouded consciousness, disorientation, disturbed circadian rhythms, thought processes and sensory disturbances, all of them fluctuating in time. The treatment combines a supportive and symptomatic approach. Benzodiazepines in supramaximal doses are usually used as drugs of choice but in some countries such as the Czech Republic or Germany, clomethiazole is frequently used as well.

Method. A computer search of the all the literature published between 1966 and December 2012 was accomplished on MEDLINE and Web of Science with the key words “delirium tremens”, “alcohol withdrawal”, “treatment” and “pharmacotherapy”. There were no language or time limits applied.

Conclusions. When not early recognized and treated adequately, delirium tremens may result in death due to malignant arrhythmia, respiratory arrest, sepsis, severe electrolyte disturbance or prolonged seizures and subsequent trauma. Owing to these possible fatalities and other severe unexpected complications, delirium tremens should be managed at an ICU or wards ensuring vital signs monitoring. In symptomatic treatment, high doses of benzodiazepines, especially lorazepam, diazepam and oxazepam are considered the gold standard drugs. Supportive therapy is also of great importance.

Key words: delirium tremens, alcohol withdrawal, treatment, pharmacotherapy, benzodiazepines

Received: February 21, 2013; Accepted with revision: November 21, 2013; Available online: December 11, 2013
<http://dx.doi.org/10.5507/bp.2013.089>

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INTRODUCTION

Due to historical and social factors, alcohol does not usually belong to the group of illicit substances. This fact makes it one of the most common drugs of abuse with enormous social and economic impacts worldwide. Alcohol plays a main role in substance use disorders and alcohol abuse represents a significant issue with increasing morbidity and mortality in the population¹⁻⁶.

Among these complications, acute withdrawal syndrome, or withdrawal delirium, may occur when blood or tissue alcohol levels decline after intake reduction or a modest period of cessation or dose reduction. Alcohol withdrawal delirium always represents one of the psychiatric emergencies. The symptoms of alcohol withdrawal delirium were first described by Samuel Pearson in 1813 as a “brain fever”. The term “delirium tremens” was introduced the same year by British physician Thomas Sutton in his book “Tracts on delirium tremens, on peritonitis, and on some other inflammatory affections, and on gout”.

METHOD

A computer search of the all the literature published between 1966 and December 2012 was accomplished on MEDLINE and Web of Science with the key words “de-

lirium tremens”, “alcohol withdrawal”, “treatment” and “pharmacotherapy”. There were no language or time limits applied. The obtained list of references to the articles was manually re-examined to find additional articles.

CLINICAL PICTURE

Alcohol withdrawal syndrome appears after a significant reduction or complete discontinuation of alcohol consumption in patients suffering from alcohol dependence. The most severe complication of alcohol withdrawal syndrome is alcohol withdrawal delirium (delirium tremens), which may be preceded or complicated by seizures. The withdrawal symptoms are caused by specific changes in brain neurophysiology after various periods of (usually heavy) drinking⁷. Alcohol withdrawal syndrome represents a group of certain symptoms that arise usually 1-3 days after the last drink⁸. Sometimes the symptoms are already present when the alcohol blood level is above 0 (0.5‰ or even more). In the mild form of the syndrome, tremor, hyperactivity, anxiety, tachycardia, sweating and sleep disturbances are present. In severe alcohol withdrawal, especially when untreated, hallucinations, seizures and delirium may occur. Even with the proper treatment, delirium tremens may be a life-threatening condition in 1-5% of patients⁹⁻¹².

Delirium is a global confusional state (in some countries, the term “qualitative disturbance of consciousness” is used). It may present as a hyperactive state with increased arousal and psychomotor activity or agitation with substantial vegetative and other psychological symptoms (disorientation, illusions, hallucinations, delusions, affective instability, irritability, attention disturbance, combativeness), typical for alcohol withdrawal delirium as described in ICD-10 criteria. In some patients, delirium manifests as a hypoactive state with decreased arousal and psychomotor activity. Although this picture is rare in alcohol withdrawal delirium, it is associated with worse prognosis, delayed diagnosis and treatment and later complications. In the remaining patients, a mixed type of delirium with fluctuations between the two types is present. Complete or fragmentary amnesia is also among the delirium symptoms.

Somatic symptoms are important components of delirium. They are present at two levels: vegetative, comprising tachycardia, blood pressure fluctuations, body temperature increase, sweating, mydriasis, hyperhidrosis, nausea, vomiting and diarrhea and accompanying CNS symptoms, comprising tremor, ataxia, dysarthria, dysphagia, agnosia, aphasia, myoclonus and epileptic paroxysms (usually generalized tonic-clonic convulsions).

Apart from DT, here are other psychiatric problems associated with withdrawal such as acute alcohol hallucinosis.

DIAGNOSIS

Contemporary diagnostic criteria for alcohol withdrawal delirium cover qualitative disturbance of consciousness, cognitive dysfunction fluctuating in time or rapidly developing perceptual disturbances. All the symptoms must emerge during, or shortly after, heavy alcohol intake cessation.

According to the ICD-10, alcohol withdrawal delirium (F10.4) is defined as alcohol withdrawal state (F10.3) complicated by delirium (F05.-); seizures may also appear.

1X.3 - Withdrawal state, general criteria

G1. Clear evidence of recent cessation or reduction of substance use after repeated and usually prolonged and/or high-dose use of that substance.

G2. Symptoms and signs compatible with the known features of a withdrawal state from the particular substance or substances.

G3. Not accounted for by a medical disorder unrelated to substance use and not better accounted for by another mental or behavioral disorder.

Alcohol withdrawal syndrome (F10.3)

A. The general withdrawal criteria must be met.

B. At least 3 of the following:

- 1) tremor of the tongue, eyelids or outstretched arms;
- 2) sweating;
- 3) nausea, retching or vomiting;

- 4) tachycardia or hypertension;
- 5) psychomotor hyperactivity;
- 6) headache;
- 7) insomnia;
- 8) malaise or weakness;
- 9) transitory visual, auditory or tactile hallucinations or illusions;
- 10) seizures – generalized, tonic-clonic.

Delirium other than induced by alcohol or other psychoactive substances (F05.-)

- A. Clouding of consciousness, i.e. reduced clarity of awareness of the environment, with reduced ability to focus, sustain or shift attention.
- B. Disturbance of cognition, manifest by both:
 - (1) impairment of immediate recall and recent memory, with relatively intact remote memory;
 - (2) disorientation in time, place or person.
- C. At least one of the following psychomotor disturbances:
 - (1) rapid, unpredictable shifts from hypo-activity to hyper-activity;
 - (2) increased reaction time;
 - (3) increased or decreased flow of speech;
 - (4) enhanced startle reaction.
- D. Disturbance of sleep or the sleep-wake cycle, manifest by at least one of the following:
 - (1) insomnia, which in severe cases may involve total sleep loss, with or without daytime drowsiness, or reversal of the sleep-wake cycle;
 - (2) nocturnal worsening of symptoms;
 - (3) disturbing dreams and nightmares which may continue as hallucinations or illusions after awakening.
- E. Rapid onset and fluctuations of the symptoms over the course of the day.

PREVALENCE

Approximately 16-26% of hospitalized patients have problems with alcohol dependence⁶. Withdrawal symptoms arise in 31% of trauma patients and in 16% of surgery patients in the postoperative period¹³⁻¹⁵.

At psychiatric wards in Germany, the annual prevalence of the diagnosis of delirium in alcohol-dependent patients was 0.6-0.7% or 4.9-7.4 (ref.^{16,17}). At departments specializing in alcohol dependence treatment, the rate of delirium tremens was 5-11% (ref.^{18,19}).

In the Finnish population, the lifetime prevalence of alcohol-induced delirium was 0.18% (95% CI 0.11-0.32%) (ref.²⁰). Other reviews showed the expectation of experiencing withdrawal delirium to be 4-15% for alcohol-dependent individuals^{21,22}.

Delirium develops in 5-20% of patients treated for alcohol withdrawal syndrome^{10,11,23,24}, with the rates varying from study to study from 1.25% to 33%.

ETIOPATHOGENESIS

The etiopathogenesis of alcohol withdrawal delirium will be mentioned briefly in this paper. Although delirium tremens is known to complicate an alcohol withdrawal state, there is no clear explanation of the fact that only 5-10% of withdrawals result in delirium²⁵. The kindling effect is considered to play an important role in delirium development²⁶⁻²⁸. According to Ballenger and Post²⁹, kindling is responsible for certain graduation of withdrawal symptoms as a function of number of previous abstinence and intoxication episodes, resulting in lower seizure threshold and CNS excitability. This represents a stimulus for the kindling process in subcortical structures (the limbic system, hypothalamus and thalamus). The more often withdrawal episodes repeat, the more severe they become and may result in seizures and delirium tremens.

Chronic exposure to ethanol results in down-regulation of inhibitory gamma-aminobutyric acid (GABA) receptors in the CNS. On the other hand, excitatory N-methyl-D-aspartate (NMDA) glutamate receptors are up-regulated in alcohol dependence. Abrupt cessation of alcohol intake results in withdrawal syndrome when this neuroadaptation is unmasked³¹. The role of benzodiazepines in alcohol detoxification is to re-establish the balance and suppress the predominance of glutamate by enhancing GABA transmission. In the United States, benzodiazepines are recommended in moderate to severe alcohol withdrawal and delirium tremens management¹¹.

The neurophysiology of GABA and glutamate transmission is identical in alcohol withdrawal delirium. An increase in noradrenaline and dopamine neurotransmission was discovered as well. Neurotoxicity, damage of CNS neurons, arousal and sympathetic activity increase resulting from oxidative stress and increased intracellular calcium influx represent common findings in delirium tremens. Benzodiazepine and clomethiazole use is also in accordance with the GABA-ergic model and has a positive influence on withdrawal and epileptic seizures.

Fig. 1. The kindling phenomenon, adapted from Post 2002 (ref.³⁰).

Delirium tremens usually develops in individuals with a history of long-term and heavy drinking^{19,20}.

COURSE

Delirium usually develops within 24-72 h as an acute or subacute complication of withdrawal syndrome³²⁻³⁷.

Throughout the day, the fluctuation of symptoms is typical with worsening in the evening and at night (disturbance of circadian rhythm or its inversion). The symptoms usually slowly subside within 1-7 days. The symptoms of withdrawal itself (as defined in the ICD-10) are often still present several days after the delirious features have fully subsided.

Despite complete or partial amnesia, the experience of delirium is traumatizing for the patient and may lead to long-term mental disorders interfering with full recovery.

COMPLICATIONS OF DELIRIUM TREMENS

Delirious patients have high morbidity and mortality rates. Mortality in the next 8 years after an episode of delirium tremens was 30.8% (HR = 1.38, 95% CI 0.43-4.48), which is comparable with patients suffering from severe malignant diseases^{20,38}.

Without proper management, mortality may range from 5% to 15% or even 20% (ref.^{23,39}). When treated appropriately (benzodiazepines) and detected early, the mortality should not exceed 1% (ref.^{11,40}).

Delirium tremens may be complicated by several severe or life-threatening conditions. When diagnosed and managed insufficiently, the morbidity and mortality rates increase, hospitalization prolongs and complications such as status epilepticus, coma or other severe psychiatric disorders such as Wernicke-Korsakoff syndrome, central pontine myelinolysis, chronic alcohol halucinosis or even dementia may develop.

As the most frequent complications, injuries (bed falls, seizures) such as fractures, intracranial hemorrhage, hypokalemia, hypomagnesemia, upper gastrointestinal bleeding, pneumonia, vomiting, aspiration with pneumonia, respiratory arrest, arrhythmias, sepsis, bed sores or death may emerge; also possible escape from the ward may result in an injury or unintentional self-injury^{32,33,36}.

TREATMENT

The management of delirium tremens represents a multidisciplinary (psychiatry, neurology, intensive and internal medicine professionals etc.) and comprehensive approach, with nurses and the patient's family being involved as well. The treatment is provided at six different levels⁴¹.

Preventive measures

According to clinical experience, thorough monitoring and prompt treatment of the withdrawal syndrome is

the best way of preventing severe complication such as delirium tremens⁴².

Many studies focus on severe alcohol withdrawal syndrome from the point of view of possible risk factors. A previous episode of delirium and/or seizures during withdrawal in the patient's history seems to be the greatest risk factor/ predictor^{10,23,24,43,44}. Other risk factors/predictors may be concurrent medical illness or infectious diseases^{10,19,40,43,45}. According to other studies, tachycardia of more than 100 or 120 beats per minute and hypertension – systolic blood pressure over 145 mmHg - above may represent potential risk factors/predictors^{23,43,44}.

There are several laboratory features showing a potential risk of delirium such as low levels of serum potassium although this finding could not be replicated in a study using subsequent multivariate analysis^{23,46,47}. According to studies using specially designed rating scales, elevated liver enzymes - alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyltransferase (GGT) - or carbohydrate-deficient transferrin (CDT) and mean corpuscular volume (MCV) can predict more severe alcohol withdrawal⁴⁸. Brathen et al. described significant relation of elevated levels of ALT, AST, ALT/AST ratio, GGT and CDT and alcohol-related seizures, with CDT being the best single marker. Low sensitivity of all these laboratory parameters impede their routine clinical use in predicting severe withdrawal^{48,49}.

A study of 182 alcohol-dependent individuals showed significant association of early emergency management and serum ALT level above 1.5-fold the upper limit and severe withdrawal symptoms²¹. In other studies, the frequency of thrombocytopenia or functional changes of platelets was much higher in patients developing delirium or seizures^{12,50}. Some studies show some connection between brain serotonin dysregulation due to monoamine oxidase (MAO) inhibition and DT development in alcohol dependent individuals^{50,51}. Changes in liver enzymes and CDT in delirious patients may, as parallel phenomena, show excessive alcohol intake. Also plasma levels of the methionine metabolite homocysteine are significantly elevated in individuals with delirium tremens as compared to uncomplicated withdrawal. Homocysteine elevation was found to be connected with withdrawal seizure activity^{52,53}.

In case of a high risk of alcohol withdrawal delirium, the use of benzodiazepines for preventive purposes may be reasonable.

There is no evidence that administration of ethanol to delirious patients or those at risk for delirium is superior or even equal in effect or side effects to benzodiazepines^{54,55}.

Patients fearing the withdrawal symptoms, can lose adherence to the treatment of their dependence when the withdrawal symptom control and management are not adequate at the very beginning^{9,56,57}. A proper detoxification program and withdrawal management can alleviate future severity of subsequent attacks of the alcohol withdrawal syndrome and help to increase the motivation for comprehensive treatment and abstinence^{9,58}. From the pharmaco-

logical point of view, benzodiazepines were found to be effective in the treatment of alcohol withdrawal, seizures and delirium tremens prevention⁵⁹⁻⁶¹. The existence of a direct antidote for benzodiazepines favors them as a drug of choice⁶².

Chlordiazepoxide in a fixed dosage (FD) schedule with gradual reduction in 8-10 days is one of the most commonly used drugs for alcohol withdrawal treatment⁸. In inpatients, some authors prefer the so-called symptom-triggered (ST) schedule to FD with a maximum loading dose of up to 30 mg of diazepam equivalent, or a front-loading regimen comprising an initial high dose followed by ST or FD (ref.^{11,63-65}). However, there is a suggestion that even in outpatients, this regimen may help to motivate the patients to start their dependence treatment^{60,61}. In a study of 165 patients, the quantity of medication, relapse time in the following 12 months, well-being or treatment satisfaction did not significantly differ in a group of patients treated with FD and those with an ST approach⁸. A recent prospective, randomized clinical trial reported no significant difference between loading or ST regimens of benzodiazepine administration in alcohol withdrawal management⁶⁶. Some authors recommend ST under 24-h medical monitoring or ICU observation^{54,64}.

Eliminating and correcting somatic complications

Early supplementation with vitamins (especially B1), glucose and fluids with electrolytes (magnesium, potassium) is vital in delirium tremens^{32,33,67-69}. When pure glucose is administered, severe cardiomyopathy or Wernicke's encephalopathy develop quickly due to the utilization of the last thiamine reserves in activated glycolysis. High doses (300-500 mg/day) of thiamine should be administered together with or prior to glucose and should not be discontinued for 7-14 days (better administered parenterally because of reduced ability to be absorbed in an oral form) (ref.^{54,70,71}).

Caring for the overall physical condition

Many factors can significantly affect the outcome, development and course of delirium. These are especially patient monitoring, safety, balanced homeostasis (hydration, nutrition), vital function support, prevention of urine and fecal retention, early mobilization, stabilization of chronic illnesses (hepatic, coagulation, anemia).

Adjusting environmental conditions

Environmental factors can influence the overall condition and should contribute to the patient's calming down. The general rules are as follows: quiet and caring environment, preferably a single room or adequate bed distance, no unnecessary objects, checks up at least four times per hour with attempts to reorient the patient and minimization of outside noise. In case of extreme agitation or aggression, mechanical restraints may be applied for as short as possible and under close monitoring to prevent harm to the self/others^{32,33,67}. A watchful and sensitive approach of the nursing personnel is absolutely important.

Symptomatic and supportive treatment

Drug doses should be as low as possible to achieve the proper effect and tranquilization and should be distributed in intermittent boluses with focus on the rapid onset and its adjustment to the general condition. Premature discontinuation of the medication may result in delirium relapse in the next 24 h. The whole treatment with gradual reduction of the medication usually takes 7-14 days.

In symptomatic therapy, benzodiazepines are the drugs of choice; in some regions, clomethiazole is used as well⁷²⁻⁷⁸. In alcohol withdrawal delirium, supportive therapy is essential as well.

There is cross-tolerance of alcohol and medication commonly used in the treatment of alcohol withdrawal¹¹. In mild or moderate symptoms of alcohol withdrawal, carbamazepine may be used as an alternative drug but its use in withdrawal delirium has not been sufficiently proved⁷⁵. Under certain conditions, other additional drugs may be used together with benzodiazepines, for example antipsychotics (haloperidol, beta-blockers, clonidine or phenytoin) (ref.⁷⁹). In case of refractory delirium, propofol has also been recently shown to be an effective adjunctive drug⁸⁰⁻⁸³.

Subsequent care

After delirium subsides, there is a great need of proper education and supportive psychotherapy for the patients and their families consisting of gentle explanation of the underlying causes, withdrawal and delirious phenomena or bizarre experiences. The therapist aims to get the patient's full understanding of delirious symptoms, to prevent shame, guilt or depreciation and to help with reintegration into their original environment. Subsequent care may have a great influence on the patient's motivation to commence the long-term and complex treatment of alcohol dependence and has an impact on further adherence.

Clomethiazole

The GABA-ergic model of alcohol withdrawal and withdrawal delirium favors benzodiazepines in the treatment. For adequate alleviation of delirious symptoms, four to six 300 mg clomethiazole capsules are administered initially and according to the current condition the dose is repeated every 2-3 h until the calming effect is achieved, with the maximum dose being 24 capsules per day. The parenteral form of clomethiazole is no longer available on the market because of many deaths due to inappropriate use, insufficient monitoring of patients or other fatal respiratory complications^{84,85}. If delirious patients are managed at ICUs where continuous vital function monitoring is available, clomethiazole doses may be increased to 7.2 g (12 g) (ref.^{32,33}). As in benzodiazepines, CNS respiratory center depression may emerge when clomethiazole is used. Additionally, there is a risk of pneumonia due to bronchial secretion accumulation. Since clomethiazole is potentially addictive, it should not be administered for more than 10 days^{67,68}. The administration of both clomethiazole and benzodiazepines must be short-term, with gradual dose reduction after a steady

state is achieved; in benzodiazepines, approximately to 15-20% of the total dose a day³⁶.

Some studies comparing clomethiazole with benzodiazepines showed its effectiveness and some of them reported shortening and generally better tolerance of treatment as well^{69,86,87}.

Benzodiazepines

The most frequently used drugs in delirium tremens management are benzodiazepines. Usually, short-acting agents are preferred (e.g. lorazepam, midazolam and oxazepam). In clinical practice, diazepam, clonazepam or chlordiazepoxide are used as well. Oxazepam and lorazepam should be preferred as drugs of choice because of their advantageous pharmacokinetics and dynamics (no active metabolites, favorable liver metabolism by conjugation/glucuronidation). Benzodiazepines (especially clonazepam and diazepam) are also beneficial in epileptic seizure management as epileptic activity is a frequent complication seen in alcohol withdrawal and withdrawal delirium (up to 30%). They are also the drugs of choice in sedative and hypnotic withdrawal deliria.

The dosage of benzodiazepines is supramaximal in delirium tremens or withdrawal state, comparing to their common use in anxiolytic or other indications (60-90 mg of diazepam equivalent a day) (ref.³²). When administered intravenously, the risk of respiratory depression is imminent and the patient should be managed at the ICU (ref.⁶⁹).

Temporarily, administration of midazolam in a continuous infusion is considered to be suitable in intensive care.

Potential complications of benzodiazepine therapy require increased vigilance of the involved clinicians. As short-acting benzodiazepines such as oxazepam or lorazepam are used in ST regimens according to the severity of withdrawal symptoms, the nursing personnel and clinicians trained in intensive care are needed to recognize potential complications (e.g. infection) or other changes in patients' condition, which may mimic or blunt withdrawal syndrome features. Long-acting benzodiazepines (i.e. diazepam, chlordiazepoxide) are commonly administered in FD regimens⁸⁸. The peril of the FD approach is seen in under- or overestimation of the total dose resulting in excessive sedation or, oppositely, loss of control of withdrawal symptoms. Additionally, in patients who are still alcohol intoxicated, unpredictable interactions with benzodiazepines (somnolence, respiratory depression or arrest and death) may emerge. That is why in such cases, continuous and careful monitoring of their condition is necessary⁸⁹.

Potential risk of abuse and addiction must be taken into consideration anytime benzodiazepines are used in withdrawal management in outpatient settings⁹⁰.

Antipsychotics

Tiaprider, an atypical D2/D3 antipsychotic agent, can be used in uncomplicated alcohol withdrawal syndrome. It is safe, with a wide therapeutic range - the doses can

vary from 300 to 1800 mg/day - and both oral and parenteral ways of administration. The total daily dose should be administered in at least 3-4 doses. It should not be used in patients with an increased risk of epilepsy because of its potential to lower the seizure threshold^{91,92}.

In delirium tremens, tiapride alone has not shown to be effective enough so its use should be limited to uncomplicated withdrawal⁹³.

Antipsychotics in delirium tremens should be used as augmentation in extremely agitated or aggressive patients, always in combination with benzodiazepines - the GABA-ergic agents are preferred. Haloperidol may be added to the medication in doses of 5-15 mg a day. Since there is a risk of arrhythmia due to the QT interval prolongation together with hypokalemia and seizure threshold lowering, that the patient should be monitored at the ICU (ref.^{11,94}). The use of haloperidol increases mortality rate.

Antiepileptics

The anticonvulsants of non-benzodiazepine type carbamazepine and oxcarbazepine with likely GABA-ergic and NMDA-blocking activity represent other drugs of possible use^{87,95,96}. Carbamazepine has been used for over 30 years to treat alcohol withdrawal as a non-addictive, non-sedating agent reducing alcohol withdrawal symptoms^{52,87}. The newer anticonvulsant oxcarbazepine, a structurally modified carbamazepine, does not carry carbamazepine's side-effects of active metabolites.

A number of studies have confirmed carbamazepine efficacy in reducing symptoms of alcohol withdrawal syndrome in the inpatient setting^{72,97-102}. Compared with benzodiazepines or clomethiazole, carbamazepine was found effective in alcohol detoxification in seven randomized controlled studies^{72,90,97-101}. The focus was mainly on alcohol withdrawal features, delirium and seizures occurrence or presence of two or all three of them together. Six of those studies demonstrated significant alleviation in clinician-rated withdrawal phenomena using fixed or tapered (over 5-9 days) regimen with 800 mg daily as an initial dose.

In four out of seven randomized controlled studies comparing the efficacy of carbamazepine and benzodiazepines in alcohol withdrawal, the frequency of seizures and delirium tremens was reported with the odds ratio for delirium [OR = 1.25 (95% CI = 0.28-5.64), $P = \text{NS}$] and seizures [OR = 0.93 (93% CI = 0.06-14.97), $P = \text{NS}$], thus showing no significant difference.

On the other hand, there are four randomized controlled trials of alcohol withdrawal management showing no effect of either oxcarbazepine or carbamazepine^{72,101,103,104}.

According to inpatient trials of clinician-rated symptoms, there is efficacy of carbamazepine in alcohol withdrawal treatment. However, due to a small sample size in comparative trials, the ability of carbamazepine to prevent delirium tremens or withdrawal seizures compared to benzodiazepines is questionable¹⁰⁵. In Barrons and Roberts's opinion, carbamazepine is effective in secondary measures of alcohol withdrawal (i.e. craving and quality of sleep) reduction and is well tolerated when used in doses

of 800 mg a day in both fixed and tapered regimens. The probable explanations for studies failing to prove the therapeutic efficacy are delayed administration of the drug, underenrollment, low dosages and a bias in outcome assessment. Due to inconsistent outcomes in two studies, the benefit of oxcarbazepine in alcohol withdrawal remains undefined. However, carbamazepine showed its effect in reduction of moderate to severe withdrawal syndrome in inpatients. Benzodiazepines should remain the drugs of first choice in severe alcohol withdrawal state.

There are studies showing the efficacy of sodium valproate in alcohol withdrawal its use is discouraged in more severe cases¹⁰⁶⁻¹⁰⁸.

There is an open trial of gabapentin, a GABA-ergic anticonvulsant, in the treatment of acute alcohol withdrawal but not delirium tremens itself, showing its effectiveness in reducing mild symptoms¹⁰⁹.

Despite the fact that other antiepileptic drugs such as topiramate and lamotrigine¹¹⁰⁻¹¹² may be successfully used in alcohol withdrawal management, there is not enough reliable evidence for their use in alcohol withdrawal delirium.

Propofol

Propofol, as a short-acting general anesthetic having good sedative and amnesic effects and a short half-time without any accumulation in the body tissues, may be administered continuously or in boluses. Apart from being beneficial in short-term anesthesia, it may be used as another possible medication in delirium tremens management in refractory cases³⁶. Due to the general anesthetic effect, its use is strictly limited to the ICU settings. However, it has shown to be effective in extremely agitated delirium unresponsive to high doses of benzodiazepines in several cases⁸³. The efficiency of propofol in alcohol withdrawal delirium is most likely due to enhancing GABA-ergic activity and NMDA receptor inhibition in the CNS (ref.¹¹³), which is in accordance with the GABA and glutamate hypothesis of delirium tremens.

Other drugs

The effectiveness of barbiturates was reported in cases of alcohol withdrawal delirium not responding to benzodiazepines³⁶. Recently, there were no significant differences found concerning the duration of delirium tremens, length of hospitalization or medical complications between phenobarbital and diazepam. Escalating bolus doses of diazepam and additional barbiturates, if necessary, reduced the need for mechanical ventilation and ICU length of stay and nosocomial infection development^{114,115}. There are case reports showing baclofen, a GABA-B agonist, to be effective in alcohol withdrawal delirium^{116,117}, but there is not enough evidence for its safe use in uncomplicated withdrawal¹¹⁸. The new α_2 agonist dexmedetomidine was successfully used as an adjunct to benzodiazepines in 18 and 20 ICU patients diagnosed with alcohol withdrawal delirium^{119,120}.

The use of these drugs is limited to case studies and cannot be routinely recommended in the treatment of alcohol withdrawal delirium.

Nursing care for patients with delirium tremens

The management of delirious patients is extremely challenging for the nursing personnel as those individuals need full-time observation in order to monitor changes in their mental condition and to prevent exhaustion, dehydration, bed sores, stools and urine retention. Patients suffering from delirium tremens are usually males in their mid-forties or fifties, meaning that they are still physically fit and strong enough to cause complications when agitated or aggressive. The assistance of hospital security guard and even mechanical restrains is therefore often needed to prevent self-harm or injuries to the staff and other patients.

CONCLUSIONS

Delirium tremens is the most severe complication of alcohol withdrawal which usually appears after longer periods of heavy drinking. This severe condition may be life-threatening and may lead to death or severe morbidity when not managed properly. The most important issue of the treatment is its prevention by early recognition of the potential risk of alcohol withdrawal and its management. When fully developed, delirium tremens is better managed at the ICU or other wards capable of monitoring the vital functions and laboratory parameters of the patients. The most effective drugs used are short-acting benzodiazepines in supramaximal doses with their sequential reduction after pacification and overall calming is achieved.

ACKNOWLEDGEMENT

Authorship contributions: BM, JP: manuscript writing; BM: figures; BM, JP, KL, KA, MC, RB, RH: data collection; BM, JP: data interpretation; BM, JP: final approval.

Conflict of interest statement: The authors state that there were no conflicts of interest regarding publication of this article.

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