Review paper

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GABAergic Psychoactive Substance-Induced Delirium: Narrative Literature Review

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Abstract - Psychoactive substance-induced delirium is delirium which occurs during or immediate after psychoactive substance intoxication, withdrawal or during the use of specific psychoactive substance. It is characterized by sudden onset of disturbed consciousness, disorientation, hallucinations, changed psychomotor activity, insomnia, acute memory impairment, violent, and bizarre behaviour. The most commonly abused psychoactive substances which may induce delirium are those acting on the major inhibitory neurotransmitter gamma aminobutyric acid (alcohol, anxiolytics, sedatives, hypnotics, and gamma - hydroxybutyrate - GHB. Psychoactive substance-induced delirium may have hyperactive, hypoactive or mixed clinical presentation. Treatment of delirium induced by psychoactive substances is carried out with antipsychotics, anxiolytics, and sedatives, but each of the listed abused psychoactive substances has its own treatment peculiarities. This narrative literature review describes the epidemiology, pathophysiology, clinical presentation, and treatment of delirium induced by intoxication and withdrawal from GABAergic psychoactive substances. The paper summarizes well-known knowledge with the latest research in psychoactive substances-induced delirium.

Key words: delirium; GABA agents; psychotropic drugs; substance-related disorders; substance withdrawal syndrome

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Introduction

Delirium is an acute brain disorder characterized by sudden onset of disturbed consciousness followed by disorientation, hallucinations, changed psychomotor activity, insomnia, acute memory impairment, violent and bizarre behaviour [1,2]. According to DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition), delirium is an acute attention and consciousness disorder with sudden onset and fluctuating intensity of aforementioned symptoms [3]. Three main types of delirium according to clinical presentation are: hyperactive, hypoactive and mixed delirium [4].

The incidence of delirium is the highest among elderly hospitalized patients undergoing surgical procedures of various indications and patients suffering dementia [3-5]. There are many causes of delirium: neurologic diseases, electrolyte disturbances, head traumas, infections, medication intake, psychoactive substances (PS) abuse [6]. The PS-induced delirium is either induced by PS intoxication or PS withdrawal [6,7].

Both ICD-10 and ICD-11 (International Statistical Classification of Diseases, 10th and 11th edition) describe PS-induced delirium,

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along with other mental disorders induced by specific PS. According to ICD-10, PS causing delirium are alcohol, opioids, cannabinoids, anxiolytics, sedatives and hypnotics, cocaine, psychostimulants, hallucinogens, tobacco, volatile solvents, and combination of the aforementioned PS [8]. In the group of PS causing delirium, ICD-11 also includes synthetic cannabinoids, synthetic cathinones, 3,4-methylenedioxy-methamphetamine, 3,4-methylenedioxyamphetamine, dissociative PS such as ketamine and phencyclidine, some medicaments [9]. While ICD-10 only describes PS-induced delirium which may occur during PS withdrawal, ICD-11 mentions the delirium occurrence both in acute intoxication and withdrawal induced by each of the aforementioned PS [8,9]. According to ICD-11, PS-induced delirium is delirium which occurs during or soon after PS intoxication, withdrawal or during the use of specific PS. The consumed quantity of specific PS in the specific period of time is capable of inducing delirium. The symptoms are not due to a primary mental disorder and another health condition [9]. DSM-5 also includes delirium in substance-induced disorders along with other substance-induced mental disorder. According to DSM-5, PS-induced delirium is also divided into PS-induced intoxication delirium or PS-induced withdrawal delirium [10].

PS-induced delirium may end fatally and presents a real diagnostic and treatment challenge for a physician due to broad differential diagnosis and inconsistent treatment guidelines [6,7,11]. According to the literature, the most commonly abused PS which may induce delirium are those acting on the major inhibitory neurotransmitter gamma aminobutyric acid (GABA). GABAergic PS are alcohol, anxiolytics, sedatives, hypnotics, and gamma - hydroxybutyrate (GHB) [6,8]. The aim of this narrative literature review is to gather and present the knowledge from the available literature regarding GABAergic psychoactive substance-induced delirium in order to facilitate recognition and treatment of this complex medical condition.

Alcohol-induced delirium

Alcohol is the most common cause of PS - induced delirium. It induces delirium either during the acute intoxication or alcohol withdrawal syndrome [6].

Alcohol withdrawal delirium is a severe complication of alcohol withdrawal syndrome. Studies suggest that 3 to 5 % of patients hospitalized for alcohol withdrawal develop withdrawal delirium [12]. The lifetime prevalence of the alcohol-induced withdrawal delirium is 0.18 % in the general population [13,14]. The syndrome appears after sudden and significant reduction of alcohol consumption in patients suffering from chronic alcohol dependence [13,15]. While there is a lot of data on alcohol intoxication induced-psychosis, the authors did not find specific epidemiological data on alcohol-induced intoxication delirium in the literature [7].

Alcohol stimulates the GABA transmission in the nervous system, producing anxiolytic effect via the GABA-A receptor [11,16]. Alcohol also exerts an anxiolytic effect by stimulating the transmission of the second most represented inhibitory neurotransmitter, glycine, mostly acting on receptors in the spinal cord and brainstem [1 7]. Furthermore, alcohol increases adenosine concentration in the synapses by blocking equilibrative nucleoside transporter 1 and then exerts ataxia and anxiolysis by adenosine binding to A1 receptors in the cerebellum, basal ganglia, and cortex [18]. Alcohol tolerance involves numerous neurotransmitter systems [19]. It seems to have a significant role in the delirium development during acute alcohol intoxication, leading to larger amounts of alcohol consumption, resulting in metabolic imbalances, including hypoglycaemia and electrolyte disorders [20]. On the other hand, alcohol withdrawal syndrome occurs due to abruptly increased glutaminergic N-methyl – D - aspartate (NMDA) receptors' activity, which are no longer affected by the inhibitory alcohol effect, and to the GABA - A desensitization induced by chronic alcohol consumption [21].

Symptoms of alcohol withdrawal syndrome occur in different timeline stages [12]. Symptoms of autonomic hyperactivity, as tremor, palpitations, sweating, arise the first-6-8 hours after the last alcohol drink. These symptoms may last several hours to 2 days. Then, psychotic symptoms may occur within 12 hours and seizures, mostly tonic-clonic, occur after 6-48 hours following the last alcohol drink [22]. Alcohol withdrawal delirium mostly occurs 72 hours after the last alcohol drink, but the whole first week is risky [12,22]. Alcohol withdrawal delirium lasts 1 to 8 days or more when progressing to refractory delirium [12,23]. The predictors of delirium during alcohol withdrawal are: systolic blood pressure above 150 mmHg, pulse rate above 100/min, recent withdrawal seizures, withdrawal delirium or seizures in the past, older age, recent misuse of other GABAergic substances, and comorbid somatic disorders [24]. In predicting the clinical severity of alcohol withdrawal syndrome with special reference to the symptoms of delirium such as perceptual disturbances, disorientation, and agitation very useful is the Clinical Institute Withdrawal Assessment of Alcohol Scale (CIWAS) [12]. Approximately 1 to 4 % of hospitalized patients die due to alcohol withdrawal delirium, mostly because of hyperthermia, cardiac arrhythmias, status epilepticus, or comorbid medical disorders [24]. Immediate mortality rate of the alcohol withdrawal delirium without proper management is 5-20 % and when treated appropriately the immediate mortality does not exceed 1 %. Mortality in the next 8 years after an episode of alcohol withdrawal delirium is 30.8 % [7].

Acute alcohol intoxication most often occurs after consumption of large amounts of alcohol [20]. The severity of alcohol intoxication depends on age and gender, amount of drink, body weight, alcohol tolerance, percentage of alcohol in consumed drink, time period of alcohol consumption, time of day, current mood, phase of menstrual cycle, liver function [20,25]. In rare cases, acute alcohol intoxication may progress to excited delirium syndrome (ExDS). It is hyperactive delirium with predominant symptoms of agitation, which occurs less frequently than in intoxications with other PS [26,27]. 4.5 % of all ExDS are distinctly induced by alcohol intoxication compared to 43 % of ExDS induced by other P S [26]. Alcohol increases GABAergic transmission in the brain and is therefore more prone to induction of hypoactive delirium, which is characterized by inhibition of psychomotor functions, apathy, acute attention deficit disorder, various quantitative consciousness disorders, increased suggestibility [28,29]. Alcohol-induced intoxication delirium is mostly associated with acute intoxication with at least one more PS [26,27,29].

Anxiolytics and sedatives, mostly benzodiazepines (BDZs) are the first line treatment of alcohol withdrawal syndrome due to their sedative, hypnotic, and anticonvulsant effects. Most commonly used are diazepam (po, iv, im), oxazepam (po), and lorazepam (po, with parenteral formulations not available in Croatia) [15,30]. Prophylactic uptake of thiamine, atypical antipsychotics, and corrections of metabolic disturbances, should also be provided [2,15]. Trazodone in dose of 50 mg seems to be a useful sedative for inducing sleep in delirious patients, but it has not yet been officially proposed in such manner [6,23]. A significant number of second-line agents have been described for the treatment of mild to moderate alcohol withdrawal syndrome, such as antiepileptics, but data are lacking for their administration in withdrawal delirium [11-13,15]. The study of Shah et al., which included 30 patients, shows that ketamine may be a useful adjuvant agent to BDZs in the treatment of alcohol withdrawal syndrome which is resistant to BDZs. Ketamine given by continuous infusion, in combination with continuous infusion of lorazepam, reduced the first withdrawal symptoms within one hour after the begin of infusion. No side effects were reported, beside transient hypertension in two patients [31].

There is no medication indicated for alcohol intoxication that is able to speed up the metabolism of alcohol. In case of agitation during alcohol intoxication, haloperidol im/

po up to 10 mg or promazine 25-100 mg im/po should be given. Correction of electrolyte imbalance and hypoglycaemia, vitamin B supplementation, and monitoring of vital functions are required [7,25]. When administrating glucose parenterally, 100 mg of vitamin B1 should be concomitantly given iv to prevent encephalopathy as both substrates are required for carbohydrate metabolism in the brain [25].

Treatment of alcohol-induced ExDS is no different from treatment of ExDS induced by any other PS. The core of treatment is symptomatic, very often provided in the Intensive Care Unit (ICU). Carefully titrated BDZs and antipsychotics are administered, with physical restraint when needed. Lorazepam (po, iv, im), diazepam (po, iv, im), and midazolam (iv, im, in) in high doses are used in the treatment of alcohol-induced ExDs. Disadvantage of BDZ use in ExDS are the synergism with alcohol in terms of excessive sedation, respiratory depression, and hypotension, so they should be carefully titrated. Both first and second generation of antipsychotics are proposed in the ExDS management, mostly haloperidol (im, iv) ziprasidone (im), and olanzapine (im) [32,33]. The dissociative agent ketamine, administered iv, im or in, has been shown to be useful in the rapid prehospital management of ExDS patients without significant adverse effects. Ketamine has a synergistic effect with BDZs; therefore, it may be proposed for rapid tranquilization, and iv BDZs are then administered for further delirium management [32,33]. However, there are currently no specific studies on the efficacy of ketamine in the treatment of alcohol-induced intoxication delirium, so further research is needed [32].

Antipsychotics are emerging as the first therapeutic line for hypoactive delirium [4], especially aripiprazole, which has been shown to be more effective in resolution of hypoactive delirium than haloperidol, also exerting less adverse symptoms. Quetiapine is also effective in treating hypoactive delirium. Case reports show the potential utility of methylphenidate in hypoactive delirium management [34].

Delirium induced by anxiolytics, sedatives, and hypnotics

Just above two percent of people aged 15 to 64 abuse anxiolytics and sedatives. The prevalence of anxiolytic abuse is equal to the cocaine abuse in the USA [35]. Anxiolytics are most commonly abused in the elderly population - consumption of anxiolytics in 20 % of people over the age of 65 is considered problematic. Of all the anxiolytics, BDZ tranquilizers are the most widely used, followed by BDZ hypnotics [36]. Seventy eight percent of patients aged 65 years or more have at least one withdrawal symptom after the cessation of BDZ or Z-hypnotics. Most common psychological symptoms are insomnia and anxiety, and the most common physical symptom is tremor [37].

Benzodiazepines - induced delirium

The study by Smarczewski and associates recorded 443 cases of medications poisoning of children over a ten-year period at the West Paraná University Hospital [38]. Sixty three percent of poisonings were accidental and 31.8 % were suicide attempts. The most common medications whose consumption has led to poisoning were BDZs, followed by analgesics [38]. Between 1996 and 2013, the number of deaths caused by BDZs intoxication increased by more than 400 %, and emergency department visits due to BDZ intoxication increased by more than 300 % from 2004 to 2011. The highest risk of BDZ intoxication is with concomitant alcohol and/or opiate use, both accidental and in suicidal intent [35].

BDZs act selectively on the BDZ binding site of subtype A on the GABA receptor, an ion chloride channel. BDZs act as allosteric modulators of the GABA A receptor, increasing the GABA affinity for the receptor and the frequency of chloride channel opening. This results in anxiolysis, sedation, decreased muscle tone, anticonvulsant effect, and anterograde amnesia. BDZs, unlike alcohol, do not interfere with other inhibitory neurotransmitters. BDZs in long-term use exert tolerance and

dependence. Tolerance occurs with all BDZs, because of intrinsic changes in receptors during long-term use of BDZs in high doses [39]. Tolerance to hypnotic and sedative effects are common, while tolerance to anxiolytic effect is not expected [40]. Tolerance leads some patients to increase the dose which may progress to intoxication resulting in delirium [10]. Tolerance and dependence most commonly occur with short-acting BDZs, mostly alprazolam [41]. Abrupt discontinuation of BDZs consumption results in decreased neuronal inhibition and increased excitation in the brain. Expression of amino3-hydroxyl-5-methyl-4-isoxazole-propionate and NMDA receptors is increased, so glutamate over-transmission in these circumstances may induce excited delirium [42]. Hypoactive delirium in the case of BDZs intoxication is due to central nervous system (CNS) depression [43].

As a consequence of chronic BDZ misuse, BDZ withdrawal syndrome may follow sudden discontinuation of BDZ consumption. It usually occurs within a few hours after last BDZ consumption and may last up to couple of weeks [15]. It is characterized by psychical symptoms: anxiety, depersonalization and derealization, sleep disorders, perceptual disturbances, suicidality, and physical symptoms: tremor, sweating, tachycardia, hypertension, mydriasis, tinnitus, gastrointestinal disorders, photophobia, hypersensitivity to stimuli. Withdrawal delirium may develop in severe cases, sometimes with hyperthermia and generalized tonic-clonic epileptic seizures [15]. BDZ-induced withdrawal delirium may also occur when a misused short-acting agent, such as lorazepam, is replaced with an equal dose of a long-acting agent, such as diazepam, which is common protocol in the prevention of BDZ withdrawal syndrome. This occurs if the dose of the short-acting BDZ is not gradually tapered and the active long-acting metabolite of diazepam has not yet been incurred, leaving the depended individual without an active GABA - A agonist [44]. BDZ-induced withdrawal delirium presents as excited delirium [44,45].

BDZ intoxication may also induce delirium [44]. Consumption of BDZ, at small to moderate extent, increase the risk of delirium. The risk of benzodiazepine intoxication delirium is higher when using higher doses of long-acting agents [45,46]. Symptoms as slurred speech, incoordination, ataxia, nystagmus, cognition impairment, severe quantitative consciousness disorders predominate [10,44]. The acute BDZ-induced intoxication delirium is very common among elderly patients. Medications are the most common reversible causes of delirium in elderly population. Among them BDZ are the most frequently consumed, along with anticholinergic agents and opioids [46]. Also, studies show that the BDZ consumption in children is a significant precipitating factor for delirium, so the use of BDZ in paediatric surgery, oncology and ICU should be reduced on minimum [47]. While hyperactive delirium is induced by BDZ withdrawal, hypoactive delirium is due to BDZ intoxication [45,47,48]. However, BDZ intoxication may also induce excited delirium [49].

The most common protocol for the management of BDZ withdrawal syndrome begins with 80 % of the total daily prescribed dose of BDZ during first 24 hours. After the start of first withdrawal symptoms 25 to 50 % of initial dose should be given. The rest of dose is administered in further 24 hours. Due to high risk for epileptic seizures during the withdrawal, carbamazepine may be preventively given in dose of 800 mg per day [15]. The second protocol includes a short half-life BDZ agent replacement with a long half-life whose dose is then gradually reduced [15,50]. Diazepam is most commonly used in this protocol, but in the treatment of alprazolam withdrawal symptoms, clonazepam is more effective [15]. The third option is to use an antidote for gradual detoxification. Flumazenil is used in several countries for gradual detoxification in chronic BDZ consumers [50,51]. It is a selective benzodiazepine antagonist which rapidly restores GABA - A receptors to baseline and reduces BDZ tolerance and dependence [50]. Because it has a short half-life, it is usually given in a slow iv/sc

infusion or in multiple slow iv boluses. The use of flumazenil is recommended for withdrawal from high doses of BDZ when gradual tapering is not effective. Available literature shows that gradual withdrawal with flumazenil causes less craving for BDZ than other withdrawal protocols [50]. There are indications that flumazenil could be used as a substitute therapy such as methadone in opiate substitution, but further research is required [50,51].

On the other hand, BDZ intoxication and BDZ-induced intoxication delirium are well-known treated with flumazenil. The total of 1 mg of flumazenil given iv over 1 to 3 minutes is usually sufficient to gain vigilance [25,49]. Some patients will require a total dose of flumazenil of up to 5 mg over 10 minutes [49]. Furthermore, flumazenil is also successful in resolving BDZ-induced delirium when BDZ are used for alcohol withdrawal. Flumazenil also shows whether delirium occurred due to alcohol withdrawal or due to the administration of BDZ in withdrawal protocol because in the latter case there is a resolution of delirium after administration of flumazenil. Flumazenil has less effect in treating hyperactive delirium because in this case there is a greater possibility that it is actually alcohol-induced withdrawal delirium. The 'diagnostic' dose of flumazenil (0.5 mg) may be given first, and if BDZ-induced delirium is diagnosed, the dose of flumazenil should be increased [43]. However, flumazenil causes complications in 0.1 to 23.4 % of cases, epileptic seizures, and supraventricular arrhythmias being the most severe [43,49,52]. Finally, the core of BDZ - induced intoxication delirium treatment is symptomatic and cessation of BDZ is mandatory [52].

Zolpidem - induced delirium

Zolpidem is a hypnotic agent also acting on GABA - A receptor, with prominent effect on sleep initiation. It is also misused and may induce delirium, especially in patients suffering alcohol use disorder. Delirium occurs both due to withdrawal, which is reported in less than 1 % of zolpidem discontinuation cases, and zolpidem intoxication [15,25,53].

Delirium due to withdrawal occurs during cessation of high doses (up to 180 mg/day) and may happen in less a day after the last zolpidem consumption. The clinical presentation is very similar to BDZ withdrawal delirium. Mattoo and associates show the case in which symptoms resolved by administration of lorazepam, 1 mg twice a day during a week [53].

Zolpidem-induced intoxication delirium may occur after consumption of 5-200 mg of zolpidem [53]. Elderly female persons are more prone to zolpidem-induced intoxication delirium due to gender-related pharmacokinetic differences (they have up to 63 % higher serum concentration of zolpidem than elderly men). Furthermore, hypoalbuminemia is a risk factor for zolpidem-induced intoxication delirium because zolpidem becomes inactive when binding to plasma proteins. Additionally, liver insufficiency is also a risk factor, because it is extensively metabolized by liver [54]. Haloperidol is used in the treatment of zolpidem-induced intoxication delirium, in doses of 0.5 mg every 12 hours up to the resolution of delirium [54].

Pregabaline - induced delirium

Pregabaline is a gabapentinoid that acts on voltage gated calcium channels stimulating GABAergic neurotransmission throughout CNS. Pregabaline is abused due to its anxiolytic and hypnotic effect, potentiation of opioid effect, and reduction of opioid withdrawal symptoms [55]. For the past 15 years, case reports have been suggesting that pregabaline may cause intoxication delirium. The most exposed are older patients with comorbidities, but delirium has also been reported in the youth. Pregabaline-induced delirium mostly occurs when it is used in high doses to relieve neuropathic pain, but it may also occur at doses up to 100 mg [56,57]. Withdrawal from pregabaline also induces delirium, so the dose of pregabaline should be gradually reduced over a minimum of one week. Treatment of pregabaline-induced intoxication delirium includes antipsychotic therapy and cessation of pregabaline [58].

GHB - induced delirium

The prevalence of GHB misuse in Europe was 0.1 % to 1.7 % in 2019. Twelve percent of all emergency care cases associated with PS misuse in Europe are due to GHB intoxication or withdrawal syndrome [59]. GHB acts on GABA - A and GABA - B receptors, inducing sedative and anxiolytic effect. However, GHB is a full agonist of GHB presynaptic receptor, so it decreases the release of GABA resulting in disinhibition of dopaminergic neurons in mesocorticolimbic neuronal circuitries, thus producing psychostimulant effects: euphoria, disinhibition, sexual stimulation, and antinociceptive effect [60,61].

GHB withdrawal syndrome includes tremor, agitation, anxiety, hallucinations, and psychosis. Symptoms last 3-21 days [62]. More than 50 % of patients who suddenly discontinue GHB consumption and do not get proper treatment develop delirium [59]. Delirium is associated with more frequent consumption of GHB before the discontinuation. It occurs if an individual consumes GHB more than every 8 hours or ≥ 30 g of GHB daily [63]. Delirium is featured with psychotic symptoms, disorientation, agitation, loss of memory, incoherent thinking, attention disorder, paranoia, insomnia, aggression, tremor, tachycardia [62-65].

GHB abuse may also lead to GHB-induced intoxication delirium. Clinical presentation may be very severe. It includes aggressive behaviour, vertigo, respiratory depression, severe quantitative consciousness disorders, myoclonus, hypothermia, metabolic acidosis. Thus, most patients with GHB - induced intoxication delirium are treated in the ICU. The diagnosis is difficult to establish as patients are mostly poly-drug users [66].

Australian study shows that more than 70 % of individuals whose deaths were associated with GHB consumption were men. The fatal outcome is more likely with the higher GHB blood concentration. In most cases, consumption of multiple PS has been reported, leading to overdose, but GHB - induced suicides are also reported [67]. More cases of delirium are induced by GHB withdrawal syndrome than GHB intoxication [59].

The management of GHB withdrawal syndrome includes BDZ or pharmaceutical GHB tapering [59]. Very high doses of anxiolytics and sedatives are needed for the management of GHB withdrawal syndrome (up to 300 mg of diazepam daily) [63]. GHB tapering appears to be more effective, because pharmaceutical GHB acts on both GABA - A and GABA - B receptors, thus completely increasing GABAergic signalization [59]. Antipsychotics as olanzapin and quetiapine should also be administered [62]. Furthermore, augmented baclofen, given 10 mg 3 times daily, decreases GHB withdrawal symptoms [68]. A short-acting a2-adrenoceptor agonist dexmedetomidine is effectively used in the management of GHB withdrawal delirium. The risk for respiratory depression is less than with BDZ. The length of treatment is the same as with BDZ [62]. Neither of studied GHB antagonists are approved for the GHB intoxication-induced delirium, so the therapy is supportive and it should be provided in the ICU [66].

Conclusion

GABAergic PS are the most commonly abused PS and epidemiological data show that their consumption is rapidly increasing. Furthermore, anxiolytics and sedatives are the most used medications, both in psychiatric and somatic wards. Due to the above, delirium induced by intoxication and withdrawal from these PS is very common in clinical practice. So, it is important to determine which PS/medication led to delirium because each of these substances has its own peculiarities in the treatment and prognosis of delirium. This paper sought to synthesize existing knowledge about the most common clinical pictures of delirium aiming to facilitate recognition and treatment of this life-threatening condition. Future research should focus on further establishment of therapeutic guidelines, especially for delirium induced by GHB due to its high incidence and fatality.

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Conflict of interest

None to declare.

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