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Novel Psychoactive Substances – GHB- and Mephedrone-Induced Delirium Treated with Olanzapine: A Case Report and Literature Review

Nove psihoaktivne tvari – delirij induciran GHB-om i mefedronom liječen olanzapinom: prikaz slučaja i pregled literature

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Abstract. ***Aim***: Delirium is a sudden disturbance in mental functioning characterized by impaired attention, reduced concentration, and disorientation. A rising cause of delirium are novel psychoactive substances (NPS) – emerging drugs designed to mimic the effects of controlled substances while evading legal restrictions. The management of NPS-induced delirium remains challenging due to the lack of established guidelines. Treatment is primarily symptomatic, managing symptoms with benzodiazepines and typical antipsychotics (mostly haloperidol). This paper highlights olanzapine as a potentially effective option for treating NPS-induced delirium, particularly in cases where gamma-hydroxybutyrate (GHB) is abused. ***Case report:*** A patient dependent on NPS (GHB and mephedrone) developed delirium due to withdrawal syndrome. The patient presented with hallucinations, disorientation, dissociative speech, agitation, insomnia, attention and concentration disturbances, and autonomic instability. In addition to the usual delirium therapy (haloperidol, anxiolytics), the patient was treated with oral olanzapine, resulting in symptom resolution. This paper demonstrates the successful treatment of NPS-induced delirium with olanzapine. ***Conclusion:*** Broad receptor binding profile of olanzapine in the brain contributes to its efficacy in alleviating hallucinations, agitation, and autonomic disturbances. However, there is a need for further research to establish optimal treatment protocols for NPS-induced delirium to ensure the best possible care for patients affected by this challenging condition.

Keywords: delirium; mephedrone; olanzapine; sodium oxybate; synthetic drugs

Sažetak. ***Cilj***: Delirij je naglo nastali poremećaj mentalnog funkcioniranja karakteriziran oslabljenom pažnjom, smanjenom koncentracijom i dezorijentacijom. Rastući su uzrok delirija nove psihoaktivne tvari (NPT) – novodizajnirane droge koje oponašaju učinke kontroliranih droga, a istovremeno izbjegavaju zakonska ograničenja. Liječenje delirija induciranog novim psihoaktivnim tvarima ostaje izazovno zbog nedostatka definiranih smjernica liječenja. Liječenje je prvenstveno simptomatsko, benzodiazepinima i tipičnim antipsihoticima (uglavnom haloperidolom). Ovaj rad ističe olanzapin kao potencijalno učinkovitu opciju liječenja delirija induciranog novim psihoaktivnim tvarima, posebno u slučajevima zloupotrebe gama-hidroksibutirata (GHB). ***Prikaz slučaja:*** Pacijent ovisan o novim psihoaktivnim tvarima (GHB i mefedron) uslijed apstinencijskog sindroma razvio je delirij. Pacijent se prezentira halucinacijama, dezorijentacijom, disociranim duktusom, agitacijom, nesanicom, poremećajem pažnje i koncentracije, autonomnom nestabilnosti. Pacijent je uz uobičajenu terapiju delirija (haloperidol, anksiolitici) liječen oralnim olanzapinom te je došlo do rezolucije simptoma. Ovaj rad pokazuje uspješnost olanzapina u liječenju delirija induciranog novim psihoaktivnim tvarima. ***Zaključak:*** Širok profil vezivanja olanzapina na receptore u mozgu pridonosi njegovoj učinkovitosti u ublažavanju

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halucinacija, agitacije i vegetativnih poremećaja. Međutim, potrebna su daljnja istraživanja kako bi se uspostavili optimalni protokoli liječenja za delirij induciran novim psihoaktivnim tvarima s ciljem pružanja najbolje moguće skrbi za pacijente pogođene ovim izazovnim stanjem.

Ključne riječi: delirij; gama-hidroksibutirat; mefedron; olanzapin; sintetske droge

INTRODUCTION

Delirium, also referred to as an acute brain syndrome, is characterized by impaired attention, reduced concentration, and disorientation. This condition typically arises due to infectious, inflammatory, metabolic, or traumatic disorders, but it can also manifest as a complication of intoxication or withdrawal from psychoactive substances (PS)[1]. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), delirium manifests as an acute onset of attention, awareness, and cognitive deficits. Psychomotor disturbance, which is additional feature of delirium, categorizes delirium into three phenotypic subtypes: hyperactive, hypoactive, and mixed delirium[2]. Both the International Statistical Classification of Diseases, 10th (ICD-10) and 11th editions (ICD-11) describe delirium as a state involving a disturbance of attention, orientation, and awareness. ICD-10 and ICD-11 distinguish between delirium stemming from the direct effects of a somatic condition and delirium induced by the effects of PS or medications[3, 4]. According to ICD-10, PS which can induce delirium are cannabinoids, tobacco, sedatives or hypnotics, cocaine, opioids, psychostimulants, volatile solvents, hallucinogens, and a combination of these PS[3]. In addition to the aforementioned PS, ICD–11 also includes synthetic cathinones, synthetic cannabinoids, 3,4-methylenedioxymeth amphetamine (MDMA) and related PS, dissociatives such as ketamine and phencyclidine, methamphetamines, and methcathinone[4]. Unlike ICD-10, which delirium primarily associates with withdrawal, ICD-11 also attributes it to intoxication[3, 4].

PS-induced delirium manifests abruptly with attention, consciousness, and cognitive deficits which fluctuate within hours to days. Patients exhibit periods of lucidity interspersed with agitation, disorientation, hallucinations, delusions and confusion, intensified during the night. Vegetative symptoms, including hypertension, tachycardia, diaphoresis, flushing, and tremors, are prevalent[1, 5, 6]. PS-induced delirium is associated with a significant symptom burden which exerts numerous complications, including death, and negatively impacts the quality of life in the long-term. Therefore, it is necessary to treat PS-induced delirium as soon as possible[5, 6]. However, there is presently no registered medication that is explicitly indicated for the treatment of delirium, especially PS-induced delirium. Haloperidol is often the first-line choice, benzodiazepines are considered for benzodiazepine or alcohol withdrawal-induced delirium, and second–generation antipsychotics are second-line therapy when haloperidol is discontinued due to side effects[5–7]. Despite this therapy, many cases of PS-induced delirium still end fatally or with persistent psychiatric and somatic complications[6, 8].

In addition to common therapy (anxiolytics, haloperidol), our patient was treated with increased doses of olanzapine which have been proposed as a treatment option for GHB-induced delirium for years. However, documented cases and clinical data regarding olanzapine efficacy in this specific context are limited.

Due to globalization and advancements in 'black market' neurochemistry, a significant concern contributing to delirium is the use of novel psychoactive substances (NPS)[9]. This category of PS includes synthetic stimulants, cannabinoids, hallucinogens, and depressants designed to bypass regulations on controlled PS by mimicking their effect, with slightly altered compounds to evade legal bans[9, 10]. This paper illustrates a case report of a patient experiencing delirium induced by withdrawal from NPS. The discussion will focus on the latest findings regarding NPS-induced delirium, including epidemiological trends, pathophysiology, symptomatology, and therapeutic approaches. While the prevalence of NPS use has been increasing, there remains a paucity of literature addressing the therapy of NPS-induced delirium[9, 10].

CASE REPORT

A 20-year-old male patient was transferred to a psychiatric clinic due to delirium induced by withdrawal syndrome after being stabilized in a nearby somatic hospital. He had presented voluntarily at the first hospital, seeking treatment for his substance use disorder. However, during observation, he developed withdrawal symptoms and subsequent delirium. He was conscious but highly agitated, exhibiting tremors throughout his body, tachycardic with hypertension. Despite the administration of intravenous diazepam (200 mg in total), the agitation persisted, requiring sedation, intubation, and mechanical ventilation. After four days of treatment in the intensive care unit, he was stable and transferred to a psychiatric clinic.

On admission to the psychiatric clinic, the patient was spatially and temporally disoriented, tense, and anxious, displaying tangential thought processes, and appeared to be under the influence of hallucinations. Rapid fluctuations in his cognitive functioning were noted, alternating between periods of coherent conversation and moments of intense delusional thinking. He engaged in conversations in Croatian and English without the presence of others in the room. His hands and tongue were tremorous, with normal vital signs. Urine toxicology revealed positive results for benzodiazepines and delta-9-tetrahydrocannabinol (THC). Further inquiry revealed a history of daily oral gamma-hydroxybutyrate (GHB) and intravenous mephedrone use over the past three years, with intermittent intravenous cocaine and heroin use, cannabis smoking, intravenous and intranasal amphetamine use, use of ephedrine nasal drops, and occasional use of high doses of zolpidem and diazepam for insomnia. Additionally, the patient confirmed currently receiving antiviral therapy following an HIV diagnosis in the past couple of years.

Initially, high doses of diazepam (up to 60 mg daily), haloperidol (10 mg daily), and quetiapine (0, 25, 50 + 50mg) were administered (Table 1). Also, oral olanzapine (10 mg daily) was administered. On the second day the patient received diazepam (90 mg daily), haloperidol (15 mg daily), quetiapine (25, 50, 200 mg) and olanzapine a 10 mg. That was also the therapeutic regimen for the third day. On the fourth day, olanzapine was increased (20 mg daily per os) and clinical improvement was observed (Table 1). The patient was calm, cooperative, and oriented, and the tremor subsided. Subsequently, haloperidol was gradually reduced to 10 mg daily on the fifth day. After a week of treatment, patient became less tense, his circadian rhythm normalized, and delu-

Table 1. The therapeutic regimen for the treatment of our patient suffering from GHBNPS-induced delirium

Day	Therapy
1	diazepam per os (up to 60 mg daily), haloperidol per os (10 mg daily) quetiapine per os (0, 25, 50 +50 mg) olanzapine 10 mg per os
2	diazepam per os (up to 90 mg daily), haloperidol per os (15 mg daily) quetiapine per os (25, 50, 200 mg) olanzapine 10 mg per os
3	diazepam per os (up to 90 mg daily), haloperidol per os (15 mg daily) quetiapine per os (25, 50, 200 mg) olanzapine 10 mg per os
4	diazepam per os (up to 80 mg daily), haloperidol per os (15 mg daily) quetiapine per os (25, 0, 100 mg) olanzapine per os a 10 mg (1,0,1)
5	diazepam per os (up to 70 mg daily), haloperidol per os (10 mg daily) quetiapine per os (25, 0, 100 mg) olanzapine per os a 10 mg (1,0,1)
6	diazepam per os (up to 70 mg daily), haloperidol per os (10 mg daily) quetiapine per os (0, 0, 125 mg) olanzapine per os a 10 mg (1,0,1)
7	diazepam per os (up to 60 mg daily), haloperidol per os (10 mg daily) quetiapine per os (0, 0, 125 mg) olanzapine per os a 10 mg (0,0,2)
8 – 13	diazepam per os (up to 40 mg daily), haloperidol per os a 5 mg (only received on the 8th day, on the 9th day is removed) quetiapine per os (0, 0, 125 mg) olanzapine per os a 10 mg (0,0,1)
14	diazepam per os (up to 15 mg daily), quetiapine per os (0, 0, 100 mg) olanzapine per os a 10 mg (0,0,1)

sions attenuated. He was conscious, calm, with a coherent thought process, predominantly focusing on his addictive issues, and exhibited a normal mood without suicidal or aggressive tendencies. Olanzapine was continued at 10 mg per day, and diazepam was gradually reduced to 40 mg per day. The patient was transferred to the sociotherapeutic department for his addiction treatment. However, he insisted on discharge, showing no motivation for long-term addiction treatment. The assessment hadn't been completed due to the patient's discharge. Following a 14-day treatment period, the patient was released with a medication regimen comprising quetiapine a 100 mg 0,0,1; olanzapine a 10 mg 0,0,1; diazepam a 5 mg 1,0,1 + 1 as needed, B vitamins, pantoprazole (40 mg daily), and antiviral therapy (Table 1).

DISCUSSION

The prevalence of GHB use varies across the world, but in most countries, the prevalence of past-year use is less than 1%[11]. However, GHB accounts for about 3.7% of all emergency cases in Europe[12] and certain populations show an increasing prevalence of use, such as men who have sex with men (20%)[11]. GHB belongs to the class of synthetic depressants, as synthetic benzodiazepines and synthetic opioids, and is widely recognized for its abuse potential[1, 11]. Its origins are rooted in legitimate medical research and applications[11, 13] as intravenous induction of anaesthesia, the treatment of narcolepsy[13, 14,] and alcohol withdrawal syndrome[15]. However, due to significant side effects such as uncontrolled movements, arrhythmia, gastrointestinal symptoms, and hallucinations, GHB did not maintain its position as a widely accepted medical treatment[11]. GHB enhances the secretion of growth hormone and prolactin[11, 14], so recreational use of GHB is increasingly popular among bodybuilders[14]. GHB is a PS of choice for sex crimes due to its potent sedative and disinhibiting effects[16]. During the 1990s, GHB became a staple of recreational settings, offering effects similar to alcohol when taken orally such as euphoria, relaxation, reduced inhibitions, and sedation[17]. Although GHB has a decades-long history of recreational use, it is still classified as a novel psychoactive substance. This stems not from GHB being newly discovered, but rather from its relatively recent classification as a controlled substance[13]. Controlling novel psychoactive substances, amongst which is GHB, is challenging due to their rapid development, online distribution, and constant changes. Standard tests often miss them, while advanced detection is slow and lacks references. Legal loopholes and the ever-changing mixture of new compounds make classification and regulation difficult[10].

GHB (both as a natural brain compound and as a synthetized PS) exhibits neuromodulatory effects at gamma-aminobutyric acid (GABA)ergic synapses in the brain[18–20]. The effects of high doses of GHB largely involve the agonistic stimulation of brain GABA-B receptors. GHB has an effect as well on GABA-A receptors, leading to a reduction of GABAergic activity[18]. GHB in lower doses promotes dopamine release via activation of GHB receptors. It was also shown to inhibit the release of norepinephrine and acetylcholine and to have the potential for increasing serotonin levels in the brain[20–22]. These mechanisms of action can have intoxicating effects, which produce feelings of euphoria and pleasure without the typical hangover that other PS often cause[20–22]. GHB's ability to further amplify the effects of alcohol and stimulants enhances its appeal in settings such as nightclubs and parties[23–25]. GHB and its analogue gamma-butyrolactone (GBL) are associated with significant adverse effects, both acute and chronic. GHB/GBL intoxication may lead to drowsiness, hypotonia, vertigo, loss of consciousness, respiratory depression, bradycardia, hypotension, and seizures[13, 19]. Chronic use of GHB/GBL can lead to dependence, with withdrawal symptoms resembling those of benzodiazepines, and alcohol[19]. Early withdrawal symptoms typically include insomnia, tremors, confusion, and nausea but as withdrawal progresses more severe symptoms may develop. A particularly severe consequence of chronic abuse is delirium, which is especially common in heavy, frequent users[19]. During chronic GHB consumption, dopamine concentrations in the brain are suppressed. However, upon abrupt discontinuation, there is a swift surge in dopamine levels, notably

Table 2. Pathophysiology of GHB chronic use and withdrawal

Receptor/Neurotransmiter	Chronic GHB Abuse	GHB Withdrawl
GABA system	downregulation of GABA system[18–22, 31] desenzitization of GHBR and GABABR[18–22, 31]	impairment of GABA feedback inhibition – sympathetic stimulation[18–22, 31] upregulation of GABAAR – anxiety and hyperalgesia[18–22, 31]
glutamate/NMDA	increase of glutamate levels initially, then downregulation of NMDARs in the frontal cortex[31]	dysregulation of glutamate signaling – neuronal hyperexcitability[31]
dopamine	hyperpolarization of dopamine neurons, decrease dopamine release in the VTA[31]	rapid increase in dopamine levels and D1 and D2 upregulation – agitation, paranoia, confusion, hallucinations[31]
serotonin	increased serotonin synthesis, release, reuptake, metabolism[31]	disruption of serotonin levels – mood disturbances, anxiety, hallucinations[31]

GABA – Gamma-Aminobutyric acid, **GHBR** – Gamma Hydroxybutyrate receptor, **GABABR** – GABA-B receptor, **NMDA** – N-Methyl-D-Aspartate **NMDAR** – NMDA receptor, **VTA** – Ventral tegmental area, **D1** – Dopamine receptor D1, **D2** – Dopamine receptor D2

in the frontal cortex and thalamus regions, stemming from an upregulation of dopamine D1 and D2 receptors[20]. Concurrently, since GHB is a GABA agonist, its withdrawal precipitates a diminished GABAergic neurotransmission, significantly contributing to the manifestation of delirium. The increased dopamine levels and reduced GABAergic transmission can lead to hyperactivity of hippocampal neurons, which is strongly believed to be associated with GHB-induced delirium[20] (Table 2). One of the first documented cases of GHB-induced delirium[22] shows a patient admitted to an acute psychiatric ward presenting with suicidal ideation and a year-long history of GHB use alongside other PS. Upon admission, the patient was hostile and exhibited severe insomnia. She displayed profound disorganization, psychosis, and uncooperativeness, with extreme irritability and distractibility. Management of her symptoms required multiple intramuscular injections of haloperidol and lorazepam and her recovery was prolonged and complicated[22]. A case report from 2016[26] demonstrates the successful use of dexmedetomidine, an alpha-2 adrenoceptor agonist, in treating GHB withdrawal delirium when benzodiazepines alone were insufficient. A 23-year-old woman presented to the emergency department with severe agitation and delirium with a history of a two-year-long GHB dependence, along with misuse of methamphetamine and benzodiazepine. The patient exhibited severe agitation, tremors, sweating, and tachycardia[26]. She was disoriented, experiencing visual and auditory hallucinations, and displayed paranoia and disorganized thoughts. Despite administering 65 mg diazepam, 50 mg quetiapine, and 10 mg olanzapine over 24 hours, her symptoms persisted. Transferred to the intensive care unit, she received a dexmedetomidine infusion and was continued on diazepam, and by the fifth day, her agitation and hallucinations had diminished[26]. A report from Denmark[27] shows the potential efficacy of electroconvulsive therapy (ECT) in treating severe delirium resistant to conventional pharmacological interventions, even amidst intensive concurrent anticonvulsive medication. Following four sessions of ECT, the patient's agitation subsided completely, and he displayed no neuropsychiatric symptoms[27].

In the aforementioned case reports, antipsychotic medications were often employed as an adjunct to the described therapies for managing delirium associated with GHB withdrawal, mostly benzodiazepines[22–27]. Antipsychotics have been a long-standing treatment modality in the management of delirium, offering a complementary approach when used alongside other interventions[28]. Haloperidol has been extensively favoured as a medication of choice due to its substantial efficacy at dopamine receptors and reduced anticholinergic adverse effects. However, due to notable side effects, particularly extrapyramidal symptoms, there has been a shift towards using atypical antipsychotics for delirium treatment[28].

In cases of GHB-induced delirium where benzodiazepine treatment alone sometimes proves inadequate, additional medication is warranted. Antipsychotics are favoured especially for patients experiencing persistent hallucinations[29]. In addition to common therapy (anxiolytics, haloperidol), our patient was treated with increased doses of olanzapine which have been proposed as a treatment option for GHB-induced delirium for years[24, 26, 29, 30]. However, documented cases and clinical data regarding olanzapine efficacy in this specific context are limited[30]. In 2007, Bennett et. Al[30] described a patient who was successfully treated with olanzapine. Their patient had been using GHB for two years. Upon admission, he presented with agitation, irritability, palpitations, and shortness of breath and developed auditory and visual hallucinations, disorganized thinking, and loose associations[30]. He was initially treated with 2 mg of haloperidol, 10 mg of lorazepam, and 5 mg of olanzapine. Due to persistent confusion and disorganization, all benzodiazepines were discontinued on the 5th day, and treatment continued with olanzapine alone. The patient's vital parameters normalized, and his hallucinations and racing thoughts diminished. Olanzapine was reduced to 2.5 mg per day and eventually discontinued upon discharge[30]. Liao et al.[24] show a case of successfully treated GHB withdrawal-induced delirium with intramuscular olanzapine. They gave intramuscular olanzapine on the 2nd and on the 4th day of delirium and the patient gradually became oriented and without delusions and hallucinations[24]. Our case also exhibited positive outcomes in managing GHB-induced delirium using olanzapine. The patient had received oral olanzapine and on the fourth day, when the olanzapine dosage was increased, our patient notably improved. He became calm, cooperative, and well-oriented, establishing and maintaining coherent contact with a reduction in psychomotor agitation, normalization of circadian rhythms, and attenuation of sensory delusions.

Olanzapine is an atypical antipsychotic that binds to multiple neurotransmitter receptors in the brain[21, 31, 32] (Table 3). One of its primary mechanisms is antagonism of serotonin 5-HT2A receptors, which is thought to be a key factor underlying its antipsychotic efficacy[31, 32]. As an inverse agonist at 5-HT2A receptors, olanzapine blocks their constitutive activity, modulating the release of dopamine, norepinephrine, and glutamate in cortical and limbic regions[22, 32]. Olanzapine also acts as an antagonist at D2 receptors, particularly in the mesolimbic pathway. This D2 receptor blockade helps reduce positive symptoms such as delusions and hallucinations. In addition to 5-HT2A and D2 receptors, olanzapine binds to several other receptors. It is a potent antagonist at histamine H1 receptors, which leads to sedation[21, 32]. Furthermore, it has a high affinity for alpha-1 adrenergic receptors and acts as an antagonist, so it is involved in the sympathetic nervous system's regulation[21, 31, 32]. Due to its broad receptor binding profile, olanzapine was useful in treating our patient's complex presentation. Its D2 and 5-HT2A receptor antagonism helped alleviate positive symptoms like delusions and hallucinations, while also potentially improving symptoms such as disorganized thinking and anxiety[31, 32]. Alpha-1 adrenergic, and histamine H1 receptor antagonism contribute to calming effects, reducing tremors and autonomic symptoms as hypertension and tachycardia related to withdrawal. Given that GHB exerts its effects

Table 3. Mechanisms of olanzapine action

Receptor	Action	Effect
5-HT2A	antagonist/inverse agonist[18, 21, 29, 31, 32]	dopamine, norepinephrine, and glutamate release modulation; reduction of hallucinations and delusions[18, 21, 31, 32]
D2	Antagonist[18, 21, 29, 31, 32]	positive symptoms reduction[18, 21, 31, 32]
H1	Antagonist[, 21, 29, 32]	sedation, calming effects[21, 31, 32]
a-1 adrenergic	Antagonist[21, 29, 32]	sympathetic nervous system regulation; reduction of autonomic symptoms[21, 32]

5-HT2A – serotonin 2A receptor, **H1** – histamine H1 receptor, **D2** – dopamine receptor D2, ***α*-1 adrenergic** – alpha 1 adrenergic receptor

through modulating the GABA system, the success of olanzapine in treating GHB-induced delirium could be attributed to its ability to influence the GABAergic neurons[29, 31] (Table 3). Serotonergic projections from subcortical regions are presumed to directly innervate and modulate the activity of GABAergic interneurons in the cortex through the 5-HT2A receptor subtype expressed on these interneurons. These interneurons can also receive direct innervation from serotonergic projections arising from the raphe nuclei, locus coeruleus, and ventral tegmental area[31]. Since one of the key mechanisms explaining GHB-induced delirium is a decrease in GABAergic inhibition, leading to neuronal hyperexcitability by binding to 5-HT2A receptors on GABAergic interneurons, olanzapine probably disinhibited these neurons, leading to an increase in GABA release and counteracted the GABAergic deficits[18, 29, 31], which proved to be significant in the effective treatment of our patient.In the case of our patient, aside from GHB, mephedrone was also consumed, which could be a contributing factor to his delirium[9]. Mephedrone is a synthetic stimulant and belongs to the cathinone class of NPS. It first gained its attention at the beginning of the 21st century when was legally available under various names like "plant feeder" and "bath salts"[33]. Approximately 0.5% of the general population uses mephedrone, but prevalence among clubbers is up to 35%[34]. Due to this initial legal status, strong euphoric effects, affordability, and easy access, mephedrone soon became a substance of abuse. It can be ingested through snorting, swallowing capsules, "bombing" (wrapping in cigarette paper and swallowing), and less commonly, rectal or intravenous administration[34]. Often used in social settings like clubs or parties, it is associated with "chemsex," where, combined with other PS such as GHB, enhances sexual experiences[18]. Because mephedrone enhances the release and inhibits the reuptake of dopamine, norepinephrine, and serotonin[35] it can cause acute toxicity, which manifests as extreme agitation, tachycardia, hypertension, hallucinations, and seizures. Additionally, long-term use may cause dependence, and severe withdrawal symptoms[19, 35]. Delirium can also result from mephedrone use, but research into this condition and its treatment is limited. Two patients who took mephedrone and experienced severe delirium were reported by Kasick et al.[36]. Their patients exhibited severe paranoia, violent behaviour, and auditory and visual hallucinations. The primary interventions with naloxone and lorazepam were unsuccessful for both, therefore benzodiazepines and antipsychotic medications had to be administered[36]. N. Bajaj et al.[25] documented a case where olanzapine effectively treated a patient suffering from hallucinations, agitation, and insomnia caused by prolonged mephedrone use which highlighted olanzapine's potential as a treatment for mephedrone toxicity[25]. Although there are currently no set protocols for treating mephedrone-induced delirium, as with any other NPS-induced delirium, it is generally advised to treat agitation and heteroagression with benzodiazepines[37, 38]. While our patient was ultimately referred to a psychiatric clinic, it is important to mention that initial management in the intensive care unit (ICU) was significant in the treatment of his delirium. The ICU allows for comprehensive care strategies like pain management, appropriate sedation, delirium screening, and early mobility. It also enables close monitoring of vital signs, rapid intervention for agitated delirium, and modification of environmental factors that can exacerbate symptoms. Such intensive care can significantly improve outcomes and potentially reduce the severity of delirium before psychiatric interventions[39]. Management of NPS-induced delirium primarily focuses on addressing the symptoms as they appear using intravenous benzodiazepines for agitation and IV fluids for hydration and electrolyte imbalance[37–41] with

Management of NPS-induced delirium focuses on intravenous benzodiazepines for agitation and IV fluids for hydration and electrolyte imbalance with haloperidol administration to minimize psychopathological experiences. Further research and case reports are needed to determine the role of olanzapine in the treatment of NPS-induced delirium, which so far has a promising effect.

haloperidol administration to minimize psychopathological experiences[40–42]. Further research and case reports are needed to determine the role of olanzapine in the treatment of NPS-induced delirium, which so far has a promising effect[25].

CONCLUSION

The increasing misuse of NPS is a major issue, with delirium resulting from intoxication or withdrawal as the most serious side effect. This paper has synthesized current knowledge on NPS-induced delirium focusing mostly on GHB and mephedrone as being one of the most commonly misused NPS. There are no definitive guidelines for the management of patients with NPS-induced delirium despite rising numbers of reported cases, leaving clinicians mainly with a symptomatic approach. Further research is needed focusing particularly on GHB, given its high incidence and potential fatality. We highlighted olanzapine as a medication of choice in treating NPS-induced delirium due to its effectiveness in successfully alleviating symptoms although the mechanisms for its therapeutic efficacy are not completely understood. It is important to further explore optimal therapeutic guidelines for treating NPS-induced delirium, ensuring the best possible care for vulnerable patients affected by this condition.

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REFERENCES

1. Lipsedge M. Excited delirium: A psychiatric review. Med Sci Law 2016;56:121-27.
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th Edition. Washington, DC: American Psychiatric Association; 2013.
3. World Health Organization [Internet]. Geneva: International Statistical Classification of Diseases, Mental and behavioural disorders due to psychoactive substance use, c2025 [cited 2024 Jul 13]. Available from: https://icd.who.int/browse10/2010/en#/F10-F19.
4. World Health Organization [Internet]. Geneva: ICD-11 for Mortality and Morbidity Statistics, MDMA or related drug-induced delirium, including MDA, c2025 [cited 2024 Jul 13]. Available from: https://icd.who.int/browse/2024-01/mms/en#1218193465.
5. Karlović D. Neurokognitivni poremećaji – delirij, demencije i amnestički poremećaj. *In*: Karlović D (ed). Psihijatrija. Jastrebarsko, Croatia: Naklada Slap, 2019;262-85.
6. Mohr AL, Friscia M, Papsun D, Kacinko S, Buzby D, Logan BK. Reports of adverse events associated with use of novel psychoactive substances, 2017–2020: a review. J Anal Toxicol 2022;46:116-185.
7. Agar MR, Amgarth-Duff I. The dilemma of treating delirium: The conundrum of drug management. Curr Treat Options Oncol 2022;23:951-60.
8. Langan C, Sarode DP, Russ TC, Shenkin SD, Carson A, Maclullich AMJ. Psychiatric symptomatology after delirium: a systematic review. Psychogeriatrics 2017;17:327-35.
9. Shafi A, Berry AJ, Sumnall H, Wood DM, Tracy DK. New psychoactive substances: A review and updates. Ther Adv Psychopharmacol 2020;10:2045125320967197.
10. Graddy R, Buresh ME, Rastegar DA. New and emerging illicit psychoactive substances. Med Clin North Am 2018;102:697-714.
11. Tay E, Lo WKW, Murnion B. Current insights on the impact of Gamma-Hydroxybutyrate (GHB) abuse. Subst Abuse Rehabil 2022;13:13-23.
12. European Union Drugs Agency [Internet]. Lisbon: Other drugs – the current situation in Europe (European Drug Report 2024). [cited 2024 May 28]. Available from: https://www.euda.europa.eu/publications/european-drug-report/2024/other-drugs_en.
13. Teter CJ, Guthrie SK. A comprehensive review of MDMA and GHB: Two common club drugs. Pharmacotherapy 2001;21:1486-1513.
14. Takahara J, Yunoki S, Yakushiji W, Yamauchi J, Yamane Y, Ofuji T. Stimulatory effects of γ-hydroxybutyric acid on growth hormone and prolactin release in humans. J Clin Endocrinol Metab 1977;44:1014-17.
15. Gallimberti L, Canton G, Gentile N, Ferri M, Cibin M, Ferrara SD et al. γ-Hydroxybutyric acid for treatment of alcohol withdrawal syndrome. Lancet 1989;2:787-89.
16. Németh Z, Kun B, Demetrovics Z. The involvement of gamma-hydroxybutyrate in reported sexual assaults: A systematic review. J Psychopharmacol 2010;24:1281-87.
17. European Union Drugs Agency [Internet]. Lisbon: GHB and its precursor GBL: An emerging trend case study. [cited 2024 May 28]. Available from: https://www.euda.europa.eu/publications/thematic-papers/ghb_en.
18. Maitre M, Klein C, Mensah-Nyagan AG. Mechanisms for the specific properties of γ-Hydroxybutyrate in brain. Med Res Rev 2016;36:363-88.
19. Health Research Bord [Internet]. Bowden-Jones O, Abdulrahim D: Guidance on the clinical management of acute and chronic harms of club drugs and novel psychoactive substances, c2024 [cited 2024 May 28]. Available from: https://www.drugsandalcohol.ie/24292/.
20. Benes FM, Berretta S. GABAergic interneurons: Implications for understanding schizophrenia and bipolar disorder. Neuropsychopharmacology 2001;25:1-27.
21. Katzung BG, ed. Basic & Clinical Pharmacology. 14th Edition. New York, NY: McGraw-Hill Education; 2017.
22. Hernandez M, McDaniel CH, Costanza CD, Hernandez OJ. GHB-induced delirium: A case report and review of the literature on gamma hydroxybutyric acid. Am J Drug Alcohol Abuse 1998;24:179-83.
23. Nicholson KL, Balster RL. GHB: A new and novel drug of abuse. Drug Alcohol Depend 2001;63:1-22.
24. Liao PC, Chang HM, Chen LY. Clinical management of gamma-hydroxybutyrate (GHB) withdrawal delirium with CIWA-Ar protocol. J Formos Med Assoc 2018;117:1124-27.

25. Bajaj N, Mullen D, Wylie S. Dependence and psychosis with 4-methylmethcathinone (mephedrone) use. BMJ Case Rep 2010;2010:0220102780.
26. Tay EM, Graham RI, Day RO. Severe GHB withdrawal delirium managed with dexmedetomidine. Med J Aust 2016;205:251-52.
27. Kjærgaard MF, Frederiksen AA, Schou TM, Clemmesen CG, Søltoft-Jensen H. Gamma-hydroxybutyric acid-induced organic delirium complicated by polydrug use successfully treated with electroconvulsive therapy: A case report. J Med Case Rep 2021;15:1-5.
28. Wang HR, Woo YS, Bahk WM. Atypical antipsychotics in the treatment of delirium. Psychiatry Clin Neurosci 2013;67:323-31.
29. Kamal RM, van Noorden MS, Wannet W, Beurmanjer H, Dijkstra BA, Schellekens A. Pharmacological treatment in γ-Hydroxybutyrate (GHB) and γ-Butyrolactone (GBL) dependence: Detoxification and relapse prevention. CNS Drugs 2017;31:51-64.
30. Bennett WRM, Wilson LG, Roy-Byrne PP. Gamma-hydroxybutyric acid (GHB) withdrawal: A case report. J Psychoactive Drugs 2007;39:293-96.
31. Kamal RM, Boekhout van Solinge T, Dijkstra BAG. The neurobiological mechanisms of gamma-hydroxybutyrate dependence and withdrawal and their clinical relevance: A review. Neuropsychobiology 2016;73:65-80.
32. Aga V, Shad M, Zhu H, Salzman C. Psychopharmacologic treatment. *In*: Stolerman IP, Price LH (eds). Encyclopedia of Psychopharmacology. Berlin: Springer Science & Business Media, 2020;1-6.
33. Winstock AR, Mitcheson LR, Deluca P, Davey Z, Corazza O, Schifano F. Mephedrone, new kid for the chop? Addiction 2011;106:154-61.
34. Papaseit E, Pérez-Mañá C, Mateus JA, Pujadas M, Fonseca F, Torrens M et al. Human Pharmacology of Mephedrone in Comparison with MDMA. Neuropsychopharmacology 2016;41:2704-13.
35. Schifano F, Albanese A, Fergus S, Stair JL, Deluca P, Corazza O et al. Mephedrone (4-methylmethcathinone; 'meow meow'): Chemical, pharmacological and clinical issues. Psychopharmacology (Berl) 2011;214:593-602.
36. Kasick DP, McKnight CA, Klisovic E. "Bath salt" ingestion leading to severe intoxication delirium: Two cases and a brief review of the emergence of mephedrone use. Am J Drug Alcohol Abuse 2012;38:176-80.
37. Wood DM, Davies S, Puchnarewicz M, Button J, Archer R, Ramsey J. Case series of individuals with analytically confirmed acute mephedrone toxicity. Clin Toxicol (Phila) 2010;48:924-27.
38. Ordak M, Maj J, Krzystanek M. Pharmacotherapy of patients taking new psychoactive substances: a systematic review and analysis of case reports. Front Psychiatry 2021;12:669921.
39. Palakshappa JA, Hough CL. How We Prevent and Treat Delirium in the ICU. *Chest* 2021;160:1326-34.
40. Schifano F, Orsolini L, Duccio Papanti G, Corkery JM. The clinical challenges of synthetic cathinones. Br J Clin Pharmacol 2020;86:410-19.
41. Tait RJ, Caldicott D, Mountain D, Hill SL, Lenton S. A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. Clin Toxicol (Phila) 2016;54:1-13.
42. Abbott R, Smith DE. The new designer drug wave: a clinical, toxicological, and legal analysis. J Psychoactive Drugs 2015;47:368-71.