CASE REPORT

Beyond Extrapyramidal Symptoms: A Case Report of Trihexyphenidyl Dependence in Patient with Major Depression and Cognitive Vulnerability

Natasha Audi Tayibnapis[1*], Satya Juwana[1], Diah Setia Utami[1], Kristiana Siste[1], Enjeline Hanafi[1], Belinda Julivia[1]

ABSTRACT

Background: Major depressive disorder with psychotic features is a severe mental disorder associated with significant functional impairment and elevated suicide risk. Clinical management becomes more complex in the presence of comorbid substance dependence and cognitive vulnerability. Trihexyphenidyl, an anticholinergic medication primarily indicated for extrapyramidal symptoms, has been increasingly misused for its euphoric effects. Dependence on trihexyphenidyl may contribute to affective instability, psychotic symptoms, and maladaptive coping, particularly when used to alleviate depressed mood. Individuals with intellectual functioning below their chronological age may have limited adaptive skills and reduced capacity for emotional regulation, further increasing vulnerability to both mood disorders and substance dependence. **Case:** We report a 24-year-old male presenting with a major depressive episode with psychotic features, recurrent suicide attempts, and long-standing trihexyphenidyl dependence. The patient had used trihexyphenidyl daily since adolescence with progressive dose escalation, withdrawal symptoms, and impaired control, primarily to obtain euphoric and anxiolytic effects. Presented clinical cognitive assessment revealed intellectual functioning below his chronological age, with impairments in abstraction, attention, language, visuospatial ability, and executive functioning. Additional diagnoses included nicotine dependence, harmful use of benzodiazepines, and recreational use of methamphetamine and alcohol. The patient received inpatient psychiatric treatment with pharmacotherapy, complemented by behavioral therapy and psychoeducation. **Discussion:** Trihexyphenidyl dependence in this patient appeared to function as a maladaptive self-regulation strategy for depressive affect and emotional distress, while cognitive limitations likely reduced adaptive coping and increased reliance on substance use. Behavioral therapy was particularly appropriate in addressing observable behaviors, reinforcing abstinence, and improving daily functioning. **Conclusion:** Assessment of nontraditional substance dependence, cognitive functioning, and tailored behavioral interventions is essential in patients with major depression with psychotic features to optimize clinical outcomes and reduce suicide risk.

Keywords: Trihexyphenidyl dependence; Major depressive disorder; Cognitive functioning; Behavioral therapy; Substance-use disorder

1. University of Indonesia, Jakarta, Indonesia

* ✉ email: natashaaudi@yahoo.com

INTRODUCTION

Major depressive disorder with psychotic features represents a severe form of mood disorder and is associated with marked functional impairment and a substantially increased risk of suicide.[1] Psychotic depression is characterized by the presence of hallucinations or delusions during depressive episodes and is consistently linked to poorer prognosis and higher rates of suicidal behavior compared with non-psychotic depression.[2] Comorbidity between major depressive disorder and substance use disorders is common and clinically significant, with evidence indicating that individuals with depression are more likely to engage in maladaptive substance use as a means of affect regulation.[3] This comorbidity is associated with greater symptom severity, increased suicidality, and poorer treatment outcomes.[4]

Among substances misused in psychiatric populations, trihexyphenidyl, an anticholinergic agent commonly prescribed for extrapyramidal symptoms, has been increasingly reported to possess abuse potential.[5] Multiple studies have described non-medical use and dose escalation of trihexyphenidyl to obtain psychotropic effects such as euphoria, mood elevation, toxic psychosis, increase social interaction, and energizing effect.[5,6,7] The prevalence of trihexyphenidyl misuse reaches 34%.[7] Repeated misuse of trihexyphenidyl may lead to tolerance, dependence, and withdrawal symptoms, including anxiety, palpitations, irritability, multiple body pains, lack of attention and concentration, lethargy and feelings of tiredness, restlessness, aggression, discomfort, craving, and isolation, which can perpetuate continued use and drug-seeking behavior.[6] These effects can complicate psychiatric presentations and require careful clinical monitoring.[7]

In addition to its abuse potential, trihexyphenidyl has been associated with impairments in intellectual performance, including memory (immediate and short-term memory) and cognitive functioning.[8] Such cognitive impairments are clinically relevant in individuals whose intellectual functioning is already below expectations for chronological age, as reduced cognitive capacity may limit insight, impulse control, and adaptive coping strategies.

Behavioral intervention, as part of Cognitive Behavioral Therapy, is widely recommended for the management of substance use disorders, particularly in individuals with cognitive limitations.[9] Behavioral interventions focus on identifying triggers, modifying maladaptive behaviors, strengthening coping skills, and reinforcing alternative, adaptive behaviors, rather than relying heavily on abstract cognitive restructuring.[10] This approach is especially suitable for patients with lower cognitive functioning, as it emphasizes concrete strategies, repetition, and environmental modification to reduce substance use and prevent relapse.

Taken together, the intersection of major depressive disorder with psychotic features, multiple drug dependence (especially trihexyphenidyl), impaired cognitive functioning, and suicidality represents a complex clinical presentation. This case highlights the importance of recognizing anticholinergic misuse in psychiatric patients and illustrates the relevance of behavioral-based interventions in managing substance dependence in individuals with cognitive vulnerability.

CASE

A 24-year-old male was admitted to an inpatient psychiatric ward due to a persistent and worsening depressed mood accompanied by suicide attempts within the preceding two weeks. The patient had experienced affective changes since April 2024 following the termination of a five-year romantic relationship due to unemployment. Since then, he reported pervasive sadness, low mood, loss of interest in previously enjoyable activities, insomnia, reduced

appetite, decreased energy, difficulty initiating daily activities, feelings of disappointment with his life, social withdrawal, fatigue, and hopelessness. In August 2024, after receiving a wedding invitation from his former partner, the patient engaged in self-harm by cutting his arm.

Over the two weeks prior to admission, the depressive symptoms intensified, culminating in suicide attempts by jumping into a nearby river and subsequently ingesting a mixture of chemical substances, including insecticide and engine oil. During depressive episodes, the patient experienced prominent psychotic symptoms, including daily auditory hallucinations of unfamiliar male and female voices commanding him to end his life, visual hallucinations of fleeting shadowy figures, and persecutory ideas, particularly in crowded environments, where he believed others were watching and speaking negatively about him.

The patient had a long-standing history of substance use involving multiple substances (**Table 1, Figure 1**). He reported regular use of trihexyphenidyl and Hexymer, nicotine, intermittent use of benzodiazepines (Riklona/Clonazepam and Alprazolam), as well as episodic use of methamphetamine and alcohol. He began using trihexyphenidyl and Hexymer in 2016 and smoking tobacco in 2015, with progressive dose escalation and difficulty stopping. When abstinent from trihexyphenidyl and Hexymer, he experienced withdrawal symptoms including anxiety, palpitations, tremor, and irritability, prompting continued use. One day prior to admission, he consumed four tablets of trihexyphenidyl and five tablets of Hexymer. He also smoked approximately ten cigarettes per day, reporting difficulty concentrating, irritability, and oral discomfort when abstinent.

Table 1. History of alcohol and substance use

Substance	Age at First Use (Year)	Pattern & Frequency of Use	Dose/ Amount	Effects Reported	Withdrawal/ Craving	Last Use Before Admission
Trihexyphenidyl	16-year old (2016)	Initially occasional (once/week); daily use since 2017 with progressive escalation	Initially 2 tablets; increased to 4 tablets/day (single intake)	Euphoria, calmness, relaxation, improved sleep	Anxiety, tremor, palpitations, irritability when not used; strong craving (10/10 → 0/10 during treatment)	1 day before admission (4 tablets)
Hexymer	16-year old (2016)	Same pattern as trihexyphenidyl; daily use	Initially 2 tablets; increased to 5–6 tablets/day (single intake)	Calmness, relief of anxiety	Same as trihexyphenidyl	1 day before admission (5 tablets)
Nicotine	15-year old (2015)	Daily smoking since 2016	~10 cigarettes/day	Calmness, relaxation	Oral discomfort, irritability, poor concentration when abstinent	1 day before admission
Alcohol	16-year old (2016)	Approximately once monthly during social gatherings	Rajawali 620 mL (19.8%) or Intisari 620 mL (17.5%),	Intoxication, relaxation, improved sleep	None reported	3 months before admission

Substance	Age at First Use (Year)	Pattern & Frequency of Use	Dose/ Amount	Effects Reported	Withdrawal/ Craving	Last Use Before Admission
			shared 4–5 people			
Cannabis	16-year old (2016)	Single lifetime use	1 joint shared	Calmness, mild pleasure	None	2016
Hallucinogens (Mushroom)	17-year old (2017)	Single lifetime use	Unknown	Amnestic episode	None	2017
Methamphetamine	18-year old (2018)	Approximately once per month, non-regular	0.25 g shared	Euphoria, wakefulness, increased energy	None	April 2024
MDMA (Ecstasy)	20-year old (2020)	Single lifetime use	Not specified	Pleasure, increased energy	None	2020
Synthetic Cannabinoids (NPS)	20-year old (2020)	Single lifetime use	Not specified	Pleasure	None	2020
Clonazepam (Riklona)	16-year old (2016)	Intermittent (once/week), non-daily	2–3 tablets per use	Calmness, reduced irritability	None reported	2 weeks before admission
Alprazolam	16-year old (2016)	Intermittent (once/week), non-daily	2 tablets per use	Calmness	None reported	3 weeks before admission
Tramadol	16-year old (2016)	Intermittent, non-regular	Up to 5 tablets per use	Calmness, reduced anxiety	None	1 week before admission
Methadone	20-year old (2020)	Single lifetime use	Not specified	Euphoria followed by discomfort	None	2020
Caffeine	Adolescence	Occasional	Up to 3 cups/day	No adverse effects	None	Ongoing

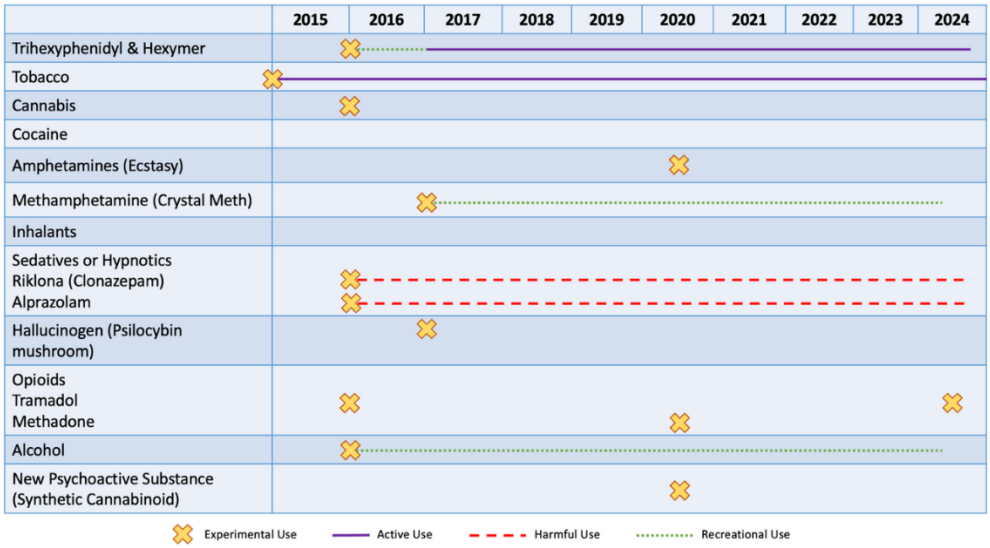

Figure 1. History of alcohol and substance use

The patient had previously sought psychiatric treatment in September 2024 at a local hospital, where he was diagnosed with trihexyphenidyl dependence and suicide attempt, and prescribed Olanzapine 10 mg daily, Fluoxetine 20 mg daily, and Diazepam 2 mg twice daily. As his symptoms did not improve, he was referred to Dr. Cipto Mangunkusumo National General Hospital and presented to the Psychiatry Outpatient Clinic on 25 November 2024, after which inpatient psychiatric treatment was initiated.

The patient was the third of six siblings and was raised in an inconsistent caregiving environment. His father was largely absent and uninvolved, while his mother displayed a permissive parenting style. Following parental separation when the patient was two years old, caregiving alternated between his mother and grandparents. The patient did not receive adequate developmental stimulation during childhood and experienced persistent academic difficulties, including grade repetition in elementary and junior high school, ultimately leading to school dropout. Subsequently, he spent more time socializing with peers and experimenting with various substances. A mental status examination was performed (**Table 2**).

Based on DSM-5, the patient reported depressed mood (hopelessness), diminished interest or pleasure, decrease appetite, insomnia, psychomotor retardation, low energy, pessimistic ideation, suicide attempt, causing significant impairment in his social and daily functioning.[11] After the occurrence of persistent mood disturbance (more than two weeks), he developed auditory hallucinations, visual hallucinations, and delusion of reference. He was diagnosed with a major depressive disorder with psychotic features (**Figure 2**). According to ICD-11, the patient had impaired control over substance use, accompanied by a subjective sensation of urge or craving to use the substance; substance use becomes an increasing priority in his life; and physiological features manifested in tolerance, withdrawal, and repeated use of the substance.[12] Therefore, he met the criteria for multiple substance dependence (trihexyphenidyl and nicotine). In ICD-10, the patient had a pattern of benzodiazepines use that is causing damage to his health (physically and mentally); hence, he was also diagnosed with harmful use of benzodiazepines.

Table 2. Mental status examination

25 November 2024	
Domain	**Description**
Appearance	Male, appears as stated age, medium build, hair covering eyes, and poorly groomed
Behavior & Psychomotor Activity	Reduced psychomotor activity, downward gaze
Attitude Toward Examiner	Cooperative
Speech	Spontaneous, low volume, clear articulation, with flat intonation
Mood	Hypothymic
Affect	Restricted, congruent
Perception	Auditory hallucinations (commanding type) and visual hallucinations present; no illusions, depersonalization, or derealization reported
Thought Process	Coherent
Thought Content	Preoccupied with substance use and smoking; pessimistic, death, self-harm, and suicidal ideation; hopelessness; delusion of reference
Cognitive Distortions	**Should statements:** “I must use trihexyphenidyl and Hexymer to get through the day”; “I must use medications to be accepted by others.” **Labeling:** “I am a failure.”

Level of Consciousness	Compos mentis Glasgow Coma Scale: Eye 4, Motor 6, Verbal 5
Orientation	**Time:** Intact; patient is able to distinguish morning, afternoon, and evening **Place:** Intact; patient recognizes current location **Person:** Intact; patient recognizes people around him
Memory	**Long-term:** Intact; able to recall past life experiences **Recent:** Intact; able to recall events from the previous day **Short-term:** Intact; able to recall three objects after 5 minutes (delayed recall) **Immediate:** Intact; able to repeat three objects immediately after presentation
Attention and Concentration	Intact; able to focus, sustain, and shift attention appropriately
Reading and Writing Ability	Intact
Visuospatial Ability	Impaired
Abstract Thinking	Impaired; patient states that 1 kg of iron is heavier than 1 kg of cotton due to perceived material differences; the movement of a pendulum attached to a string in motion was controlled by the hand holding the string; unable to engage in hypothetico-deductive thinking, as evidenced by difficulty discussing situations related to substance use in terms of possible outcomes and solutions; unable to imagine the placement of a "third eye" and provide a rationale for placing it on the head **(the patient's intellectual functioning was under his chronological age)**
General Knowledge	Partially intact; patient knows the name of the President of Indonesia but is unable to differentiate between the city and province of current residence
Impulse Control	Adequate during examination; impaired in relation to substance use behavior
Judgment	**Religious Judgment:** Impaired; patient acknowledges religious obligations but is unwilling to perform them **Legal Judgment:** Intact; patient understands legal consequences of possessing illicit drugs and expresses reluctance to re-engage in such behavior **Social Judgment:** Intact; patient behaves politely during the interview **Reality Testing Ability (RTA):** Impaired
Insight	Grade 3; patient recognizes substance use problem but attributes it to difficult life circumstances
Reliability	Generally reliable
Stage of Change	Precontemplation (for trihexyphenidyl use and smoking)
Readiness Ruler	Importance: 2/10; readiness: 0/10
Mini Mental State Examination (MMSE)	25 (impairment in the domains of orientation and visuospatial ability)
The Montreal Cognitive Assessment (MoCA)-INA	18 (impairment in executive function, visuospatial ability, attention, language, and abstract thinking)
Montgomery Asberg Depression Rating Scale (MADRS)	35 (severe)
Suicide risk score	11 (high)

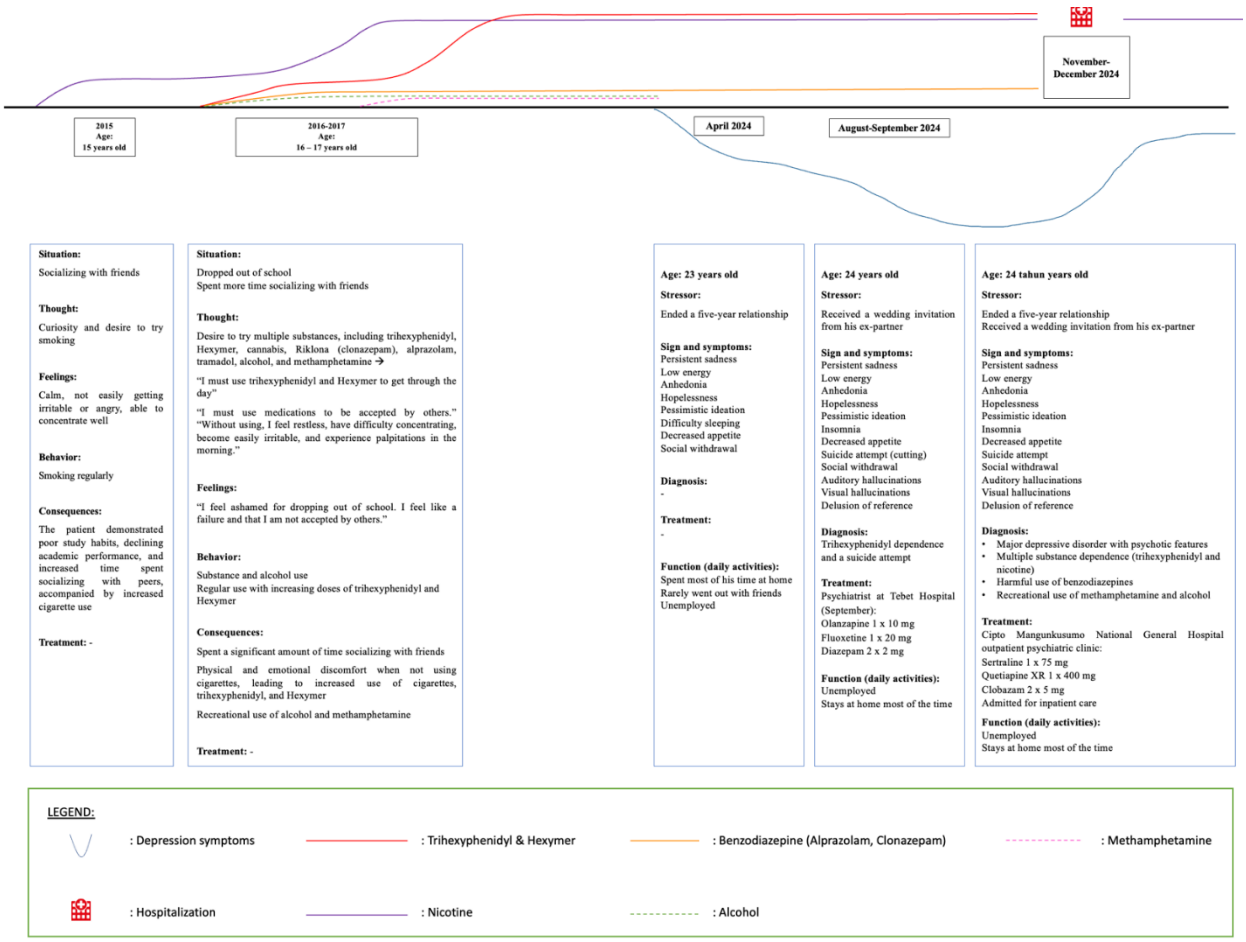

Figure 2. History of present illness

The patient had no current medical conditions. Prior to hospitalization, there was no history of chronic or recurrent medical illness. The patient had psycho-socio-economic problems, including relationship difficulties following the termination of a five-year romantic relationship, a permissive parenting style exhibited by the mother, the absence of stable employment resulting in financial difficulties, and a peer environment characterized by substance use with access to psychoactive substances (a high-risk environment). Using the Global Assessment of Functioning (GAF) scale, the patient's impaired psychological condition resulted in significant difficulties in occupational and social functioning, with a current GAF score of approximately 60. Over the past year, the patient was intermittently able to fulfill functional roles, including occasionally assisting his mother or father with work, leaving the house to socialize with friends, and maintaining interpersonal relationships within his environment. Therefore, the highest level of functioning in the past year (Highest Level of Past Year, HLPY) was estimated to be 80.

During inpatient hospitalization, the patient was given pharmacological treatment, adjusted from Sertraline 50 mg to 75 mg daily (on the third day), Quetiapine extended-release 200 mg to 300 mg (on the eleventh day) to 400 mg daily (on the fourteenth day), and Clobazam 5 mg twice daily. We also gave psychoeducation to the patient and family regarding the patient's mood condition (severe depressive episode with psychotic features) and substance-related disorders involving trihexyphenidyl, nicotine, benzodiazepines, methamphetamine, and alcohol; the treatment plan during inpatient care, including pharmacological and non-

pharmacological interventions (treatment goals, dosage, and potential side effects); the continuity of care plan for outpatient treatment, for both the patient and family (with the mother as the primary caregiver), including access to psychiatric services, restriction of financial access, management of peer environment, engagement in meaningful daily activities, and future employment planning; and the role of the family in supervising medication adherence and limiting the patient's access to psychiatric medications or substances that may be misused.

At the beginning of treatment, the patient continued to experience a desire to use substances, particularly trihexyphenidyl, especially in the morning due to feelings of anxiety manifested as hand tremors and palpitations (10/10). The patient was taught Progressive Muscle Relaxation (PMR) techniques and received Motivational Enhancement Therapy (MET) and Motivational Interviewing (MI), particularly while the patient was in the precontemplation stage of substance use, with the aim of fostering doubt and increasing awareness of the risks and problems associated with substance use behavior by expressing empathy, supporting self-efficacy, providing affirmations, reflective listening, and summarizing; maintaining and enhancing the patient's motivation to change; strengthening the patient's commitment to change; and reviewing strategies to achieve behavioral change. We implemented Behavioral Therapy (BT) for patient with SUD and intellectual vulnerability by identifying triggering situations, emotions, thoughts, and physical sensations associated with substance use; identifying coping mechanisms to manage substance cravings, including relaxation techniques, talking with others, and creating a list of structured daily activities. We follow the steps from Schijven et al. by asking simple questions to the patient and repeating them when necessary, teaching refusal skills for substance use offers by giving the patient scenario of common situation he faced before (specific settings) and role playing, repeatedly taught concepts to ensure understanding, also encouraging focus on specific goals, such as not using money to purchase substances.

Table 3. Mental status examination at discharge

27 December 2024	
Domain	**Description**
Appearance	Male, appears as stated age, medium build, hair combed, and well groomed
Behavior & Psychomotor Activity	Seated calmly, maintained appropriate eye contact
Attitude Toward Examiner	Cooperative
Speech	Spontaneous, medium volume, clear articulation, with varied intonation
Mood	Euthymic
Affect	Appropriate, congruent
Perception	No auditory hallucinations (commanding type) and visual hallucination; no illusions, depersonalization, or derealization reported
Thought Process	Coherent
Thought Content	Ways to change behavior when he is discharged from hospital; no pessimistic, death, self-harm, and suicidal ideation; no delusion of reference

Cognitive Distortions	**No should statements: "I can try to start the day without using substance and try to regulate my emotions using skills that I learned during hospitalization"** **No labeling:** "I can still try to seek employment in accordance with my capabilities and not accepted for one does not mean I am a failure"
Level of Consciousness	Compos mentis Glasgow Coma Scale: Eye 4, Motor 6, Verbal 5
Orientation	**Time:** Intact; patient is able to distinguish morning, afternoon, and evening **Place:** Intact; patient recognizes current location **Person:** Intact; patient recognizes people around him
Memory	**Long-term:** Intact; able to recall past life experiences **Recent:** Intact; able to recall events from the previous day **Short-term:** Intact; able to recall three objects after 5 minutes (delayed recall) **Immediate:** Intact; able to repeat three objects immediately after presentation
Attention and Concentration	Intact; able to focus, sustain, and shift attention appropriately
Reading and Writing Ability	Intact
Visuospatial Ability	Impaired
Abstract Thinking	Impaired; the patient's intellectual functioning was under his chronological age
General Knowledge	Partially intact
Impulse Control	Adequate during examination
Judgment	**Religious Judgment:** Impaired; patient acknowledges religious obligations but still unwilling to perform them **Legal Judgment:** Intact; patient understands legal consequences of possessing illicit drugs and expresses reluctance to re-engage in such behavior **Social Judgment:** Intact; patient behaves politely during the interview **Reality Testing Ability (RTA):** Intact
Insight	Grade 5; patient understands he has substance use problem, factors attributes to his condition, and chose to do it before. Yet, after hospitalization he wants to change and stop using substance.
Reliability	Generally reliable
Stage of Change	*University of Rhode Island Change Assessment Scale* (URICA) 13,3 (preparation for trihexyphenidyl use and smoking)
Readiness Ruler	Importance: 10/10; readiness: 10/10
Montgomery Asberg Depression Rating Scale (MADRS)	17 (mild)
Suicide risk score	2 (low)

As treatment progressed, the patient gradually became able to understand the problems related to his substance use and his capacity to change the behavior. The patient was able to weigh the advantages and disadvantages of change by exploring ambivalence and alternatives, identifying reasons for change, and increasing self-confidence. He also began to set goals and develop realistic post-discharge plans

regarding substance use behavior, including managing social interactions with peers who use substances, strategies for refusing substance offers, and establishing structured and meaningful daily activities to reduce internal and external triggers that could provoke substance use.

Craving to use substances gradually decreased (from 8/10, 5/10, 1/10, and reached 0/10 by the end of treatment). The patient was able to recognize the benefits of abstaining from substances and the disadvantages of continued use. He reported readiness to abstain from substance use (10/10) and perceived abstinence as highly important (10/10). The patient's mental status examination at discharge was summarized in **Table 3**.

DISCUSSION

This case highlights the multifactorial interplay of developmental, psychosocial, and substance-related factors underlying the emergence of severe mood pathology and multiple substance dependence. The onset of substance dependence during adolescence, a critical period for identity formation, increased the patient's vulnerability to addiction, particularly in the context of limited parental supervision and a permissive caregiving style. The absence of a paternal figure who provided guidance and value internalization further contributed to inadequate behavioral structuring during childhood. As a result, the patient sought emotional regulation, a sense of purpose, and social acceptance through substance use, which provided temporary feelings of pleasure and calmness while alleviating negative emotions. These reinforcing effects likely strengthened substance-seeking behavior and contributed to the progression of multiple substance dependence alongside severe depressive symptoms with psychotic features.

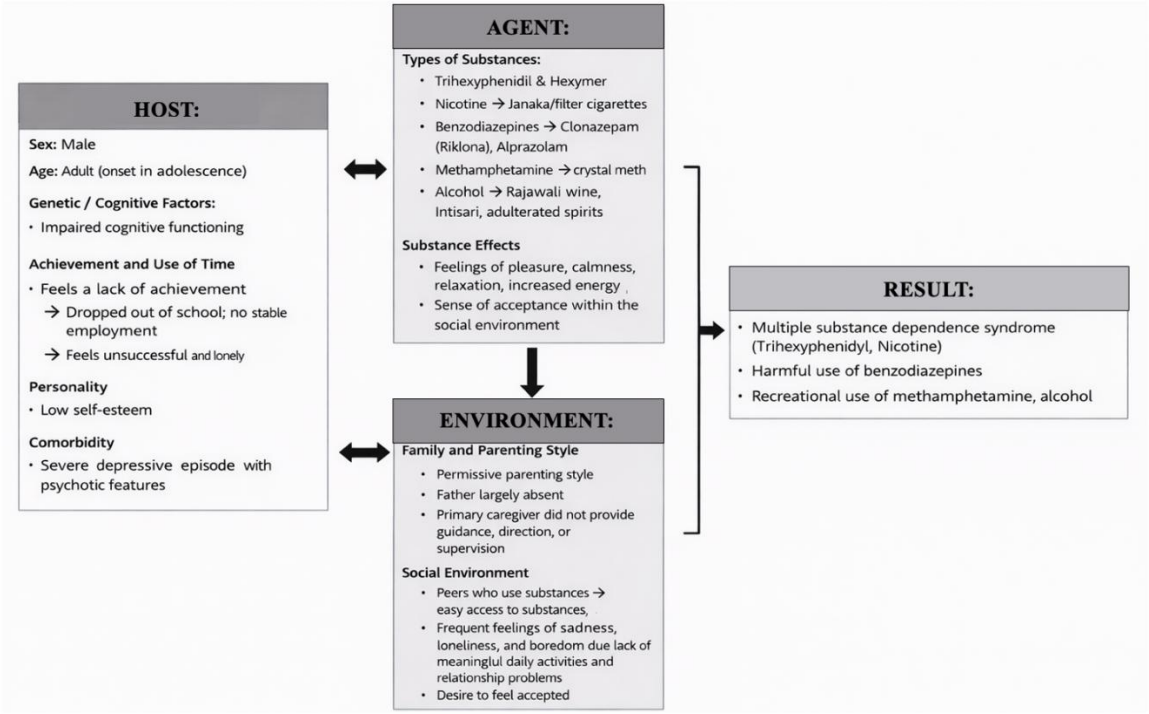

Figure 3. The epidemiological triad[13]

The patient's substance misuse behavior can be understood through behavioral learning theory, cognitive theory, and contemporary models addressing

contributing factors. From a behavioral perspective, substance use is explained by operant conditioning, in which behaviors that are followed by reinforcing consequences are more likely to be repeated — a mechanism that underlies maladaptive substance use and its maintenance.[14] Initially, the patient engaged in substance use as experimentation to obtain pleasure or to alleviate discomfort, particularly feelings of shame related to academic difficulties, grade repetition, and school dropout. This behavior was subsequently maintained by reinforcing consequences. Experiences of pleasure, calmness, and improved social interaction that led to social acceptance functioned as positive reinforcers, encouraging continued substance use. Over time, substance use increasingly served to avoid negative internal states such as anxiety, palpitations, tremors, irritability, difficulty concentrating, and oral discomfort, reflecting a pattern of negative reinforcement. In addition, attempts to reduce or discontinue substance use resulted in withdrawal symptoms, including restlessness, physical discomfort, impaired concentration, and irritability, which further reinforced continued use.

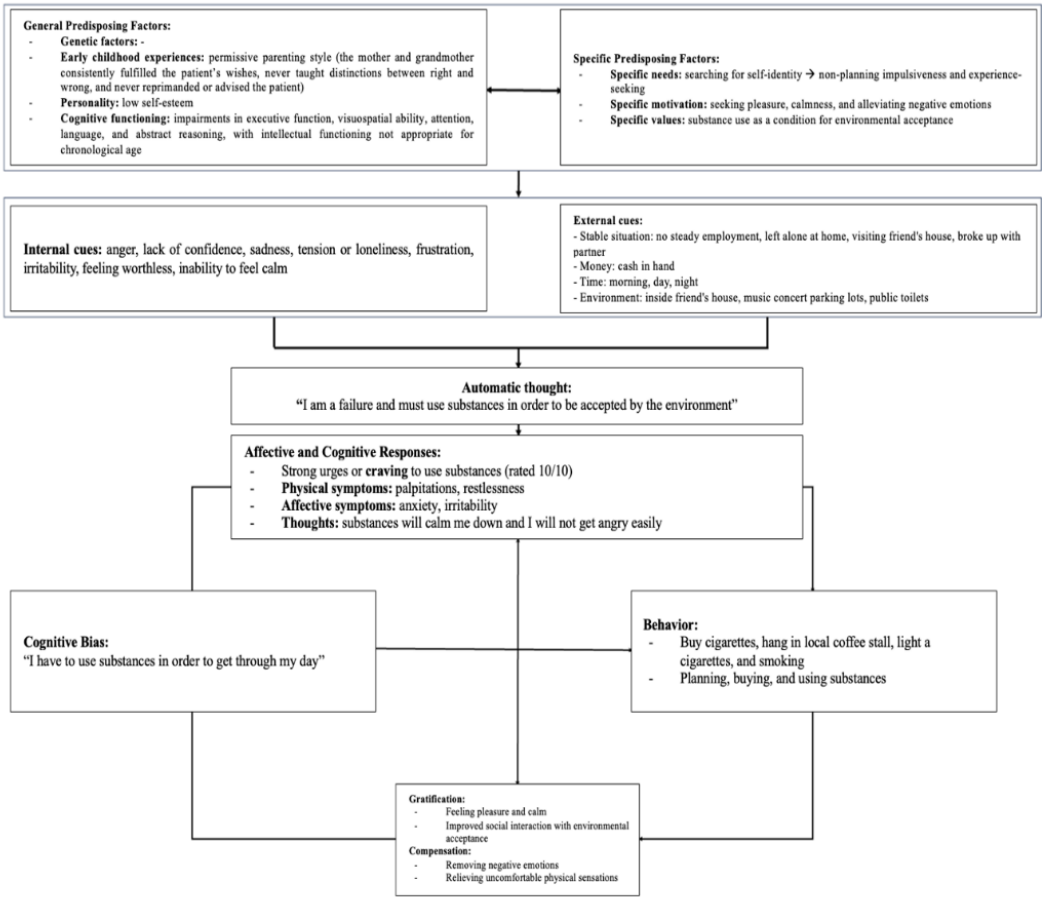

Figure 4. Cognitive-behavior model[10]

The patient's substance use can also be explained through classical conditioning, in which previously neutral environmental or contextual stimuli become conditioned triggers for substance use after repeated pairing with drug effects.[15,10] Situations that were initially neutral, such as being alone at home, visiting friends, nighttime, waking in the morning, attending entertainment venues, and having money available, became conditioned stimuli after repeated pairing with substance use. Internal cues, including

anger, low self-confidence, boredom, sadness, tension, loneliness, frustration, irritability, feelings of worthlessness, and an inability to feel calm, as well as external stressors such as relationship problems, financial difficulties related to unemployment, and a substance-using peer environment, triggered automatic thoughts and cognitive biases that intensified craving and directly led to substance use as a conditioned response. Cognitive and behavioral aspects of the patient's substance misuse align with cognitive-behavioral theory, which integrates classical and operant learning processes with cognitive processes such as expectancies, automatic thoughts, and coping responses. According to cognitive-behavioral models, substance-related behaviors are learned and maintained through interactions between reinforcing effects and cognitive appraisals, and interventions targeting these processes focus on identifying and modifying maladaptive thoughts and behaviors
.

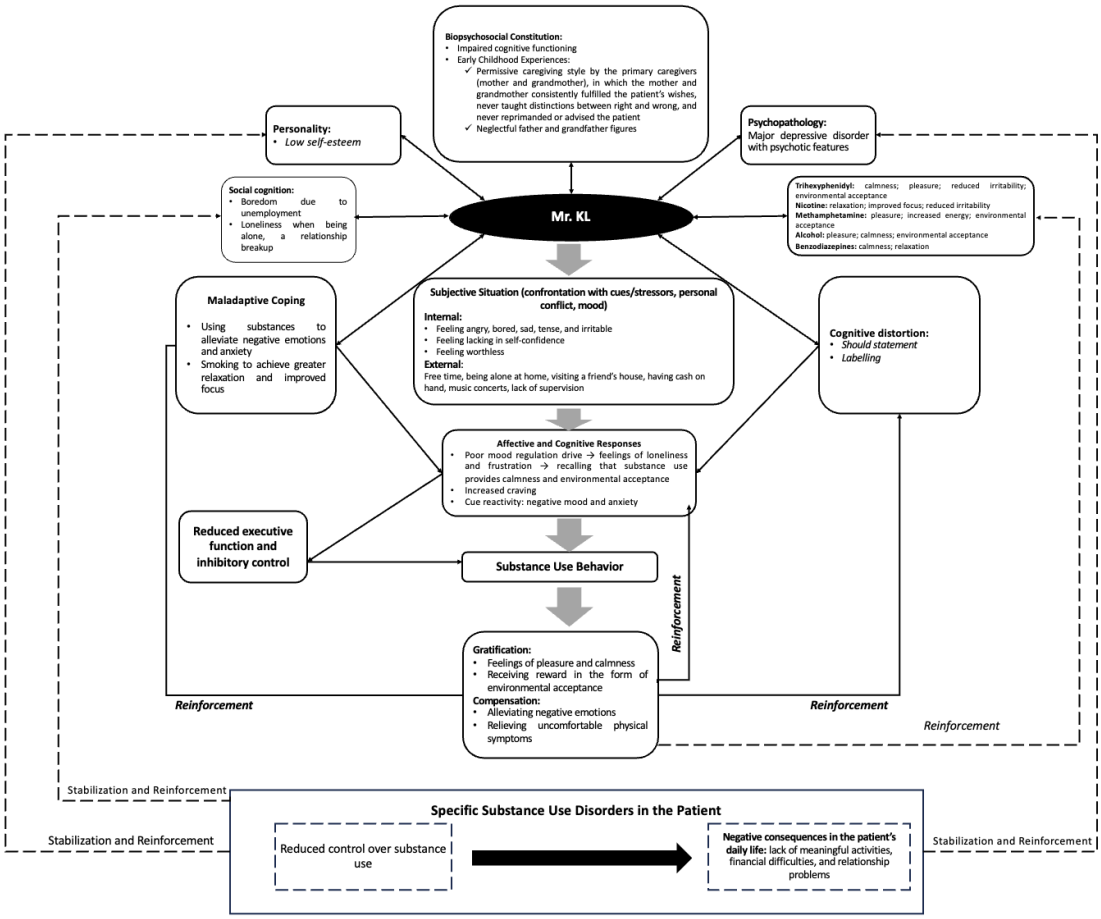

Figure 5. I-PACE model[16]

In addition, the patient's behavior is consistent with the Interaction of Person–Affect–Cognition–Execution (I-PACE) model proposed by Matthias Brand. Within this framework, predisposing personal factors, affective and cognitive responses, and executive functioning interact dynamically. External stressors and internal negative emotional states heightened reactivity to substance-related cues and craving, particularly when emotional regulation was impaired. Recurrent substance use in response to strong urges contributed to reduced executive control, diminished self-regulation, and ultimately the development of substance dependence.

Furthermore, Trihexyphenidyl is an anticholinergic medication commonly used for the management of extrapyramidal symptoms in patients receiving antipsychotics. However, several studies have reported that trihexyphenidyl has the potential to be misused through dose escalation to obtain psychotropic effects, including sensations of relaxation or pleasure, increased energy, mood elevation, and facilitation of social interaction.[18,19] A previous study by Qureshi et al. identified several risk factors for trihexyphenidyl misuse, including male sex, young adulthood, smoking, low educational background, joint family structure, low socioeconomic status, high psychosocial stress, urban residence, unemployment, and unmarried status.[6] The prevalence of trihexyphenidyl misuse varies, ranging from 1.1% in the general population to as high as 34% in psychiatric settings.[20]

The mood-stimulating and euphoric effects of trihexyphenidyl may lead to habituation or chronic dependence.[20] These effects can be explained by inhibition of dopamine reuptake and storage due to muscarinic receptor blockade. At higher doses, trihexyphenidyl also increases affinity for dopamine receptors in the limbic area, which may stimulate the central nervous system reward system and produce a “high” effect. Tolerance to these effects develops rapidly, leading individuals to escalate doses to achieve the desired effects.[19] In individuals using high doses of trihexyphenidyl, intoxication may occur, presenting with symptoms such as dry mouth and mucosa, mydriasis, decreased bowel sounds, flushed hot skin, urinary retention, constipation, agitation, tachycardia, hypertension, tachypnoea, and fever. In more severe overdose, life-threatening conditions such as hypotension, arrhythmias (including supraventricular tachycardia), respiratory depression, and cardiac disturbances may occur. Neurological and psychiatric manifestations include drowsiness, sedation, ataxia, amnesia, coma, as well as paranoia, hallucinations, delirium, and confusion.[5] Acute overdose or toxic states may occur within one hour of ingestion and generally resolve within 24 hours.[5,21]

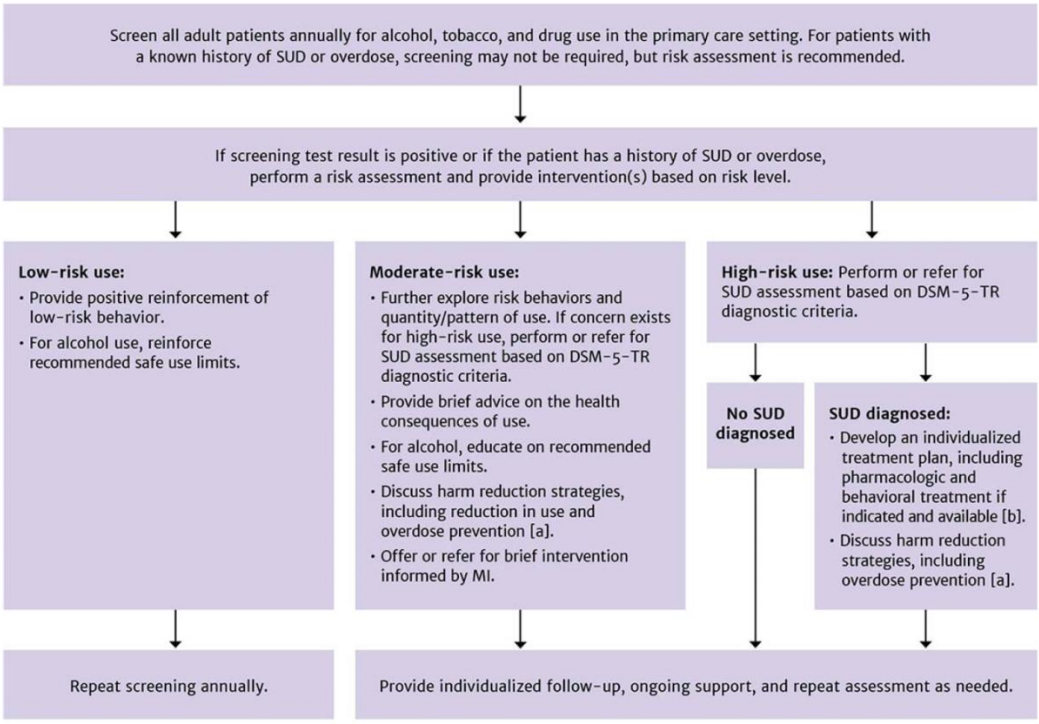

Figure 6. Substance use screening, risk assessment, and use disorder diagnosis in adults[17]

As an anticholinergic agent, trihexyphenidyl may impair intellectual performance, including memory, attention, and other cognitive functions.[8] Trihexyphenidyl-induced cognitive deficits may be related to its effects on the prefrontal cortex, which is involved in executive functioning. Resting-state imaging studies have demonstrated alterations in neural activity reflected by amplitude of low-frequency fluctuations (ALFF) of 0.01–0.08 Hz in blood oxygen level-dependent (BOLD) brain signals. These neuroimaging findings indicate impairment of the frontoparietal network (FPN), which is associated with executive cognitive dysfunction. Additional involvement of other disrupted regions, such as the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), and orbitofrontal cortex (OFC), further contributes to cognitive impairment, with the VLPFC playing a role in decision-making and goal-directed behavior, and the OFC in emotional regulation and inhibitory control.[22]

Moreover, anticholinergic misuse may lead to withdrawal symptoms.[19] Acute anticholinergic withdrawal symptoms vary and may include movement disorders, mood symptoms such as depression or dysphoria, anxiety, worsening psychopathology, motor agitation, hallucinations, gastrointestinal disturbances, physical complaints, and even neuroleptic malignant syndrome.[19,20] These symptoms may be explained by hypersensitivity of acetylcholine receptors as a response to long-term anticholinergic use. Ruberg et al. reported increased acetylcholine receptor density in the frontal lobes and alterations in nigrostriatal cholinergic receptors among individuals misusing anticholinergics.[19] Anticholinergics act competitively to inhibit acetylcholine at muscarinic receptors and, at high doses, may also block nicotinic receptors, which are involved in motor control, including at the neuromuscular junction.[20] Cholinergic receptor hypersensitivity resembles cholinergic excess observed in parkinsonism, leading to various movement dysfunctions.[19]

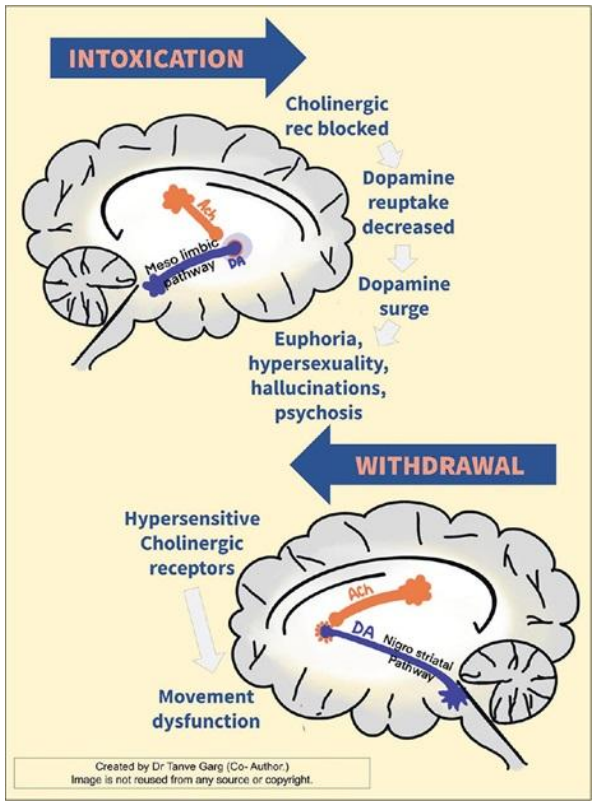

Figure 7. Mechanisms of anticholinergic intoxication and withdrawal[19]

Previous case reports of trihexyphenidyl misuse have demonstrated both psychological and physiological dependence, resulting in drug-seeking behavior and withdrawal symptoms. Withdrawal manifestations include anxiety, tachycardia, excessive sweating, irritability, tension, headache, and photophobia. These symptoms promote trihexyphenidyl-seeking behavior and subsequent dose escalation.[21] Abrupt discontinuation of trihexyphenidyl is not recommended, as it may precipitate severe withdrawal symptoms.[8] Recommended management options include tapering the dose by 1 mg every two weeks, or following recommendations from the University of Sydney and Macquarie University, which suggest slow tapering by reducing the dose by 25% over one to four weeks depending on withdrawal severity, and discontinuing trihexyphenidyl two weeks after reaching the lowest dose. Tapering is

recommended to be conducted over at least three months. Non-pharmacological interventions include occupational therapy, physical exercise, and social support. If tapering is ineffective, switching to another anticholinergic agent with fewer side effects may be considered.[19,23]

Motivational Interviewing (MI) may also be applied to patients with substance misuse who have intellectual disabilities, such as those with intellectual functioning not appropriate for chronological age. MI techniques include open-ended questions, affirmations, reflective listening, and summarizing, delivered in a more directive manner to help patients identify and express feelings related to potential change.[24] Patients with intellectual impairment often experience difficulties with refusal skills and impulse control; therefore, communication issues should be addressed using role-playing, visual aids or pictures, therapeutic games, and participatory activities. Behavioral interventions may include:[24,25]

1. Asking simple questions and repeating them when necessary
2. Teaching refusal skills for substance use offers
3. Avoiding generalizations and explaining refusal strategies in specific settings
4. Asking patients to repeat taught concepts to ensure understanding
5. Using role-playing techniques
6. Encouraging focus on specific goals, such as not using money to purchase substances.

Theme's	Objectives
Week 1 About you	Meeting each other, establishing security and trust. Room and time to make participants feel at ease. Explaining the personality profile and recognition of participants' own situation in a positive way. A small step to the consequences for behaviour.
Week 2 Effect	Setting individual long-term goals for the intervention and show the participants that small steps are needed to achieve these goals. Understanding that risky behaviour can stand in the way of achieving these long-term goals.
Week 3 What precedes?	Identification of thoughts and feelings that precede behaviour and learning to recognize these signals. Learning participants to realize that there is a moment to make a different choice.
Week 4 The challenge	Participants make a personalized change plan that helps them to cope differently with their behaviour. This includes specific actions for the participant and people in his/her environment to support him/her.
Week 5 Evaluating the change plan	Evaluating the change plan and if necessary adapt it. Specific focus on success and positive reinforcement.

Figure 8. Preventive programs for patients with mild intellectual disability or borderline intellectual functioning[26]

CONCLUSION

This case illustrates that trihexyphenidyl misuse may extend beyond its conventional use for managing extrapyramidal symptoms and develop into a clinically significant substance dependence driven by its psychoactive and mood-modulating effects. In this patient, trihexyphenidyl was primarily used to achieve calmness, pleasure, and social acceptance, contributing to dose escalation, withdrawal symptoms, and impaired control over use.

Intellectual vulnerability, characterized by cognitive functioning below chronological age and impairments in executive and adaptive functioning, appeared to increase susceptibility to substance misuse by limiting effective coping strategies, insight, and impulse control. This vulnerability underscores the importance of assessing cognitive functioning when evaluating substance use patterns in patients with severe mood disorders.

Behavioral Therapy played a central role in management by focusing on observable behaviors, trigger identification, development of alternative coping strategies, and reinforcement of abstinence, making it particularly suitable for patients with cognitive limitations. The integration of behavioral interventions with motivational approaches contributed to a reduction in craving and improved readiness for change.

This case highlights the need for increased clinical awareness of anticholinergic misuse in psychiatric settings, particularly among cognitively vulnerable individuals. Early identification, cautious prescribing, and the use of tailored behavioral-based interventions are recommended in similar cases to prevent progression to dependence and to support sustained recovery.

ACKNOWLEDGEMENTS

The authors would like to express their gratitude to everyone contributed to this case report. Informed consent was obtained from the patient and his mother prior to publication. We also thank the Department of Psychiatry and the inpatient psychiatric ward staff for their support during the clinical management of this patient. Special appreciation is extended to the supervising consultants for their guidance in case formulation and manuscript preparation.

REFERENCES

1. Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJL, et al. Burden of Depressive Disorders by Country , Sex , Age , and Year : Findings from the Global Burden of Disease Study 2010. 2013;10(11).
2. Gaudiano BA, Miller W, Herbert JD. The Treatment of Psychotic Major Depression : Is There a Role for Adjunctive Psychotherapy ? 2007;271–7.
3. Davis L, Uezato A, Newell JM, Frazier E. Major depression and comorbid substance use disorders. 2008;14–8.
4. Hunt GE, Malhi GS, Man H, Lai X, Cleary M. Prevalence of comorbid substance use in major depressive disorder in community and clinical settings, 1990-2019: Systematic review and meta-analysis [Internet]. Journal of Affective Disorders. Elsevier B.V.; 2020. 1990–2019 p. Available from: https://doi.org/10.1016/j.jad.2020.01.141
5. Chiappini S, Mosca A, Miuli A, Semeraro FM, Mancusi G, Santovito MC, et al. Misuse of Anticholinergic Medications: A Systematic Review. Biomedicines [Internet]. 2022 Feb 1 [cited 2024 Dec 28];10(2):355. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC8962297/
6. Qureshi NA, Al Amri AH, Abdelgadir MH, El-Haraka EA. Trihexyphenidyl (Artane) Dependence: A Controlled Investigation between Users and Abusers. Ann Saudi Med [Internet]. 1997 [cited 2024 Dec 28];17(2):185–90. Available from: https://www.annsaudimed.net/doi/10.5144/0256-4947.1997.185
7. Mahal P, Nishanth KN, Mahapatra A, Sarkar S, Balhara YPS. Trihexyphenidyl Misuse in Delusional Disorder. 2019;428–30.
8. Kajimura N, Mizuki Y, Kai S, Suetsugi M, Yamada M, Okuma T. Memory and cognitive impairments in a case of long-term trihexyphenidyl abuse. Pharmacopsychiatry [Internet]. 1993 [cited 2024 Dec 28];26(2):59–62. Available from: https://pubmed.ncbi.nlm.nih.gov/8378414/
9. Gosens LCF, Otten R, Didden R, Poelen

EAP. Evaluating a personalized treatment for substance use disorder in people with mild intellectual disability or borderline intellectual functioning : A study protocol of a multiple baseline across individuals design. Contemp Clin Trials Commun [Internet]. 2020;19(March):100616. Available from: https://doi.org/10.1016/j.conctc.2020.100616

10. Copersino ML. HHS Public Access. 2018;91–8.
11. Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5).
12. Saunders JB. Substance use and addictive disorders in DSM-5 and ICD 10 and the draft ICD 11. 2017;
13. Merikangas KR, Avenevoli S. Sheppard Kellam , Chair IMPLICATIONS OF GENETIC EPIDEMIOLOGY FOR THE PREVENTION OF SUBSTANCE USE DISORDERS. 2000;25(6):807–20.
14. Queiroz A De, Miguel C, Yamauchi R, Simões V, Silva CJ, Laranjeira RR. From Theory to Treatment : Understanding Addiction from an Operant Behavioral Perspective. 2015;5(8):778–87.
15. Otto MW, Ph D, Cleirigh CMO, Ph D. Attending to Emotional Cues for Drug Abuse : Bridging the Gap Between Clinic and Home Behaviors. 2007;(April):48–55.
16. Brand M, Wegmann E, Stark R, Müller A, Wöl K, Robbins TW, et al. Neuroscience and Biobehavioral Reviews The Interaction of Person-A ff ect-Cognition-Execution (I-PACE) model for addictive behaviors : Update , generalization to addictive behaviors beyond internet-use disorders , and speci fi cation of the process character of addictive behaviors. 2019;104(May):1–10.
17. New York State Department of Health AIDS Institute. Substance Use Screening , Risk Assessment , and Use Disorder Diagnosis in Adults. 2024;(May):2024.
18. Mahal P, Nishanth KN, Mahapatra A, Sarkar S, Balhara YPS. Trihexyphenidyl Misuse in Delusional Disorder. J Neurosci Rural Pract [Internet]. 2018 Jul 1 [cited 2024 Dec 28];9(3):428. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC6050776/
19. Garg T, Rawat VS. Trihexyphenidyl Use Disorder and Withdrawal Syndrome. J Psychiatry Spectr [Internet]. 2024 Jan [cited 2024 Dec 28];3(1):53–5. Available from: https://journals.lww.com/jops/fulltext/2024/03010/trihexyphenidyl_use_disorder_and_withdrawal.9.aspx
20. Baslam A, Azraida H, Aboufatima R, Ait-El-Mokhtar M, Dilagui I, Boussaa S, et al. Trihexyphenidyl Alters Its Host's Metabolism, Neurobehavioral Patterns, and Gut Microbiome Feedback Loop—The Modulating Role of Anacyclus pyrethrum. Antioxidants [Internet]. 2024 Jan 1 [cited 2024 Dec 28];13(1):26. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10812446/
21. McInnis M, Petursson H. Trihexyphenidyl dependence. Acta Psychiatr Scand [Internet]. 1984 [cited 2024 Dec 28];69(6):538–42. Available from: https://pubmed.ncbi.nlm.nih.gov/6741602/
22. Wang HY, Hao X, Lu R, Li T, Pu L, Liu W, et al. Effects of trihexyphenidyl on prefrontal executive function and spontaneous neural activity in patients with tremor-dominant Parkinson's disease: An fNIRS study. Parkinsonism Relat Disord. 2022 Dec 1;105:96–102.
23. Raji Saheed O. Trihexyphenidyl abuse in psychiatric outpatient clinic of a general hospital in Northern Nigeria. J Addict Med Ther Sci. 2020 Mar 26;6(1):003–8.
24. Bhatt N V, Gentile JP. Co-occurring intellectual disability and substance use disorders. AIMS Public Heal [Internet]. 2021 [cited 2025 Jan 1];8(3):479. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC8334640/
25. Gosens LCF, Otten R, Didden R, Poelen EAP. Evaluating a personalized treatment for substance use disorder in people with

mild intellectual disability or borderline intellectual functioning: A study protocol of a multiple baseline across individuals design. Contemp Clin Trials Commun. 2020 Sep 1;19.

26. Schijven EP, VanDerNagel JEL, Otten R, Lammers J, Poelen EAP. Take it personal! Development and modelling study of an indicated prevention programme for substance use in adolescents and young adults with mild intellectual disabilities and borderline intellectual functioning. J Appl Res Intellect Disabil [Internet]. 2020 Jan 1 [cited 2025 Jan 1];34(1):307. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7820965/