

PREVALENCE AND SYMPTOMATOLOGY OF DEPRESSION AMONGST PATIENTS WITH CNS DEPRESSANTS USE

Dr. Sheema Mustafa¹, Dr. Muhammad Ilyas², Brig. Dr. Shoaib Ahmed³, Dr. Ayesha Nadeem⁴, Dr. Fareea Mahmood⁵, Dr. Sakina Naseer⁶

¹ Post Graduate Trainee (FCPS-II), Dr. A. Q. Khan Centre Institute of Behavioral Sciences, Dow University of Health Sciences (DUHS), Karachi, Pakistan.

² Assistant Professor, MBBS, FCPS, Dr. A. Q. Khan Centre Institute of Behavioral Sciences, Dow University of Health Sciences (DUHS), Karachi, Pakistan.

³ Executive Director, MBBS, FCPS, DPM, Dr. A. Q. Khan Centre Institute of Behavioral Sciences, Dow University of Health Sciences (DUHS), Karachi, Pakistan.

⁴ Post Graduate Trainee (FCPS-II), Dr. A. Q. Khan Centre Institute of Behavioral Sciences, Dow University of Health Sciences (DUHS), Karachi, Pakistan.

⁵ Post Graduate Trainee (FCPS-II), Dr. A. Q. Khan Centre Institute of Behavioral Sciences, Dow University of Health Sciences (DUHS), Karachi, Pakistan.

⁶ Post Graduate Trainee (FCPS-II), Dr. A. Q. Khan Centre Institute of Behavioral Sciences, Dow University of Health Sciences (DUHS), Karachi, Pakistan.

ABSTRACT

Objective: To determine prevalence and symptomatology of depression amongst patients with CNS depressants use in tertiary care hospital of Karachi, Pakistan.

Materials And Methods: This cross-sectional study was carried out at the Department of Psychiatry, the Institute of Behavioral Sciences, DUHS, Karachi over a period of Six months from the approval of the research protocol (REF NO. 3952/DUHS/Approval/2025/202), date 22nd May 2025 from 1st June 2025 to 30th November 2025. All patients meeting the inclusion criteria and visiting the Institute of Behavioral Sciences, DUHS, Karachi were included in the study. After obtaining informed consent, participants completed the self-scoring Beck Depression Inventory to assess depression. Data was recorded in the attached proforma and used electronically for research purposes. All patients meeting the inclusion criteria and visiting the Institute of Behavioral Sciences, DUHS, Karachi were included in the study. After obtaining informed consent, participants completed the self-scoring Beck Depression Inventory to assess depression. Data was recorded in the attached proforma and used electronically for research purposes.

Results: The age of the patients ranged from 18 to 80 years with a median of 46. In the gender distribution, 136 (63.3%) were classified as male while 79 (36.7%) were classified as female. Depression was present in 20.5% of the patients, affecting a total of 44 individuals.

Conclusion: It is to be concluded that a notable presence of depression among patients, with males being the predominant group affected. Opiates emerged as the most commonly used substance, followed by sedatives and alcohol. These findings emphasize the importance of addressing mental health concerns, particularly depression, in individuals using CNS depressants to improve overall treatment outcomes.

KEYWORDS: Central Nervous System, Depressants, Depression, Prevalence, Symptomatology

INTRODUCTION

Mental, neurological and substance use (MNS) disorders are one of the leading causes of disability worldwide. Contributing to 14% of the global burden of disease [1]. Depressive disorders are extremely common, and it has been estimated that approximately 17% of community residents experience a major depressive episode during their lifetime [2]. According to a study, World Health Survey, conducted with 245,404 adults from 60 countries reported a 3.2% ICD-10 prevalence of depression [3]. The prevalence rates of depression were reported to be higher in low- and middle-income countries (LMICs) such as 10.3% in Malaysia [4], 45.9% in Pakistan [5], 15.1% in India [6]. Depressive disorders are often accompanied by significant anxiety symptoms or full anxiety disorders. Approximately 50% of patients with a major depression episode also experience an anxiety disorder within a 6-12-month period [7]. Alcohol use disorder (AUD) and depressive disorders are among the most prevalent psychiatric disorders and co-occur more often than expected by chance. Depressive disorders are the most common psychiatric disorders among people with AUD [8]. Among people in treatment for DSM-IV AUD, almost 33% met criteria for major depressive disorder in the past year, and 11% met criteria for dysthymia. However, major depressive disorder is the most common co-occurring disorder among people who have AUD, partly because it is among the most common disorders in the general population [8]. Depression may be a critical factor in the initiation and maintenance of opioids. According to a study

conducted in US in 2005, more opioid users reported symptoms suggestive of depression than those not taking opioids (43.6% vs 26.8%) [9].

Benzodiazepines (BZD) misuse and abuse is a serious public health problem. BZD use has also been shown to be associated with use of multiple psychotropic drugs, higher rates of depression and anxiety. [10] Benzodiazepines are psychoactive drugs used primarily to treat anxiety and sleep disorders. Their intended uses include anxiolytic, sedative hypnotic, anticonvulsant, and muscle relaxant therapy in low to medium doses [11].

A recent study was conducted that examined the prevalence of depression and anxiety among patients with substance use disorder and their association with quality of life. This study found a high prevalence of depression among patients with substance use disorder, including those using CNS depressants. It also highlighted the negative impact of depression and anxiety on the quality of life of these individuals [12].

Another study found out the relationship between depression and prescription opioid misuse in patients with chronic pain. This systematic review and meta-analysis concluded that there is a significant association between depression and prescription opioid misuse among patients with chronic pain. The study suggests that depression may contribute to opioid misuse in this population [13].

A longitudinal study By Coupland (2020) was conducted on Benzodiazepines, Z-drugs, and the risk of depression. This longitudinal study found an increased risk of depression among individuals prescribed benzodiazepines and Z-drugs, which are CNS depressants commonly used to treat anxiety and sleep disorders. The study highlights the importance of monitoring for depression in patients using these medications [14].

The association between alcohol use disorder and depression in primary care patients was studied by, Serafini (2021). This systematic review and meta-analysis concluded that there is a strong association between alcohol use disorder and depression among primary care patients. The study emphasizes the need for integrated screening and management of both conditions in primary care settings [15]. Emotion deregulation was identified as a potential underlying factor contributing to these symptoms. The study suggests the importance of addressing emotion regulation in treatment interventions for this population [16].

Therefore, this study is designed to determine the frequency and symptomatology of depression among individuals with CNS depressant use, as very little work has been done on this in Pakistan. Increasing rates of CNS depressant use, new reliable and accurate prevalence data will aid prescription practices and lead to more critical appraisals of when these drugs are necessary or should be discontinued. Existing literature might not specifically address the intersection of depression and CNS depressant use comprehensively. While there may be studies on depression or on CNS depressants individually, there is a gap in understanding how these two factors interact. Existing studies have utilized different methodologies, target different populations, or focus on different aspects of depression or CNS depressant use. Our study contributed by providing a more comprehensive understanding across different methodology, and populations.

MATERIAL & METHODS

STUDY DESIGN

Descriptive Cross-Sectional Study.

STUDY SETTING

Department of Psychiatry, Institute of Behavioral Sciences, DUHS, Karachi.

DURATION OF STUDY

Six months after the approval of the synopsis from *1st June 2025 to 30th November 2025*.

SAMPLE SIZE

With confidence level of 95%, prevalence of depression of 16.8%¹ amongst patients, margin of error 5% then a sample of least 215 patients was required.

SAMPLING TECHNIQUE

Non-Probability, Consecutive Sampling.

SAMPLE SELECTION

INCLUSION CRITERIA

- Age 18 - 80 years.
- Either gender.
- Patients diagnosed with CNS depressants use for at least 3 months, who gave voluntarily consent for the study.

EXCLUSION CRITERIA

- Depression prior to substance use.
- Patients with psychiatric illness.
- Patients who had medical illness (any terminal illness, brain injuries) were excluded from the study.

DATA COLLECTION

After the approval of the study from the College of Physicians and Surgeons Pakistan and the ethical review committee of the institute, a total of 215 patients was included in the study. Consent was obtained prior to the inclusion of patients in the study after explaining the purpose, procedure, risk, and benefits of the study. They were ensured for confidentiality. A brief account of name, age, gender, marital status, ethnicity, education, family size, number of substances use patients in family, employment status, and socioeconomic status were recorded on predesigned semi-structured proforma (Annex B). All the patients meeting the selection criteria were included in this study from the outpatient and inpatient departments of Dr. AQ Khan

Centre, Institute of Behavioral Sciences, Department of Psychiatry, DUHS, Karachi.

Participants were asked to respond on self-scoring Beck Depression Inventory in a friendly and conducive environment. Depression was labelled as described in the operational definition.

DATA ANALYSIS

The data collected was analyzed using the computer package SPSS (Statistical Packages of Social Sciences) version 22.0. Mean and standard deviation (SD) were computed for quantitative variables age and monthly income. Frequency and percentage were calculated for gender. Marital status, ethnicity, education status, type of substance use, occupational status, and depression. Depression was stratified for age, gender, place of residence, marital status. Monthly income, and occupation. Post-stratification, Chi-square test, and t-test was applied. P-value < 0.05 was taken as significant.

RESULTS

In this study, 215 patients were included to determine the prevalence and symptomatology of depression among individuals using CNS depressants at a tertiary care hospital in Karachi, Pakistan. The analysis revealed the following: The age of the patients ranged from 18 to 80 years with a median of 46 with an interquartile range of 29 and C.I (38.41----42.68) as shown in **TABLE 1**.

TABLE # 1. DESCRIPTIVE STATISTICS OF AGE n=215

DESCRIPTIVE		Statistics	
AGE (years)	Median	46.00	
	95% Confidence Interval for Mean	Lower Bound	38.41
		Upper Bound	42.68
	5% Trimmed Mean	40.07	
	Minimum	18	
	Maximum	80	
	Range	62	
	Interquartile Range	29	
	Skewness	0.032	
	Kurtosis	-1.107	

The monthly income of the patients ranged from 18000 to 90000 PKR with a median of 27000 with an interquartile range of 32000 and C.I (35534.32----41228.48) as shown in **TABLE 2**.

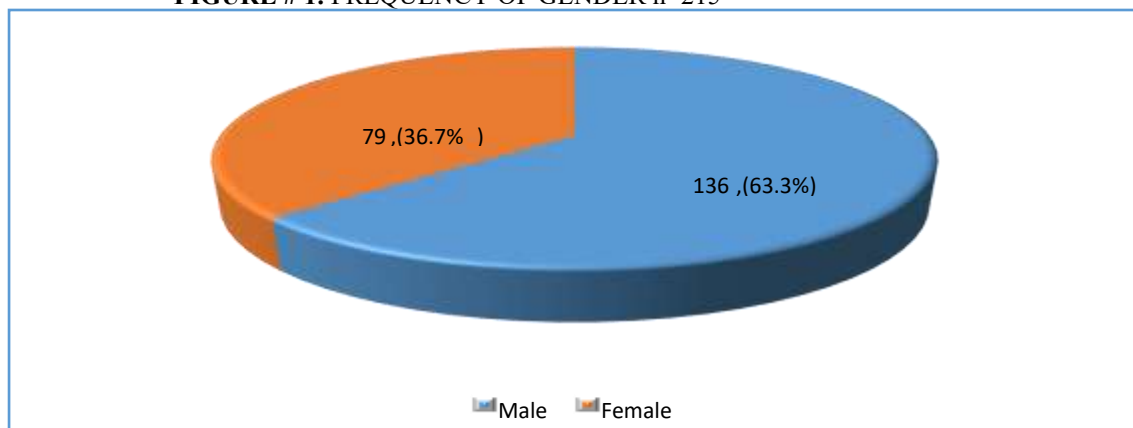
TABLE # 2. DESCRIPTIVE STATISTICS OF MONTHLY INCOME n=215

DESCRIPTIVE	Statistics
-------------	------------

MONTHLY INCOME (PKR)	Median	27000.00	
	95% Confidence Interval for Mean	Lower Bound	35534.32
		Upper Bound	41228.48
	5% Trimmed Mean	36645.99	
	Minimum	18000	
	Maximum	90000	
	Range	72000	
	Interquartile Range	32000	
	Skewness	1.058	
	Kurtosis	0.047	

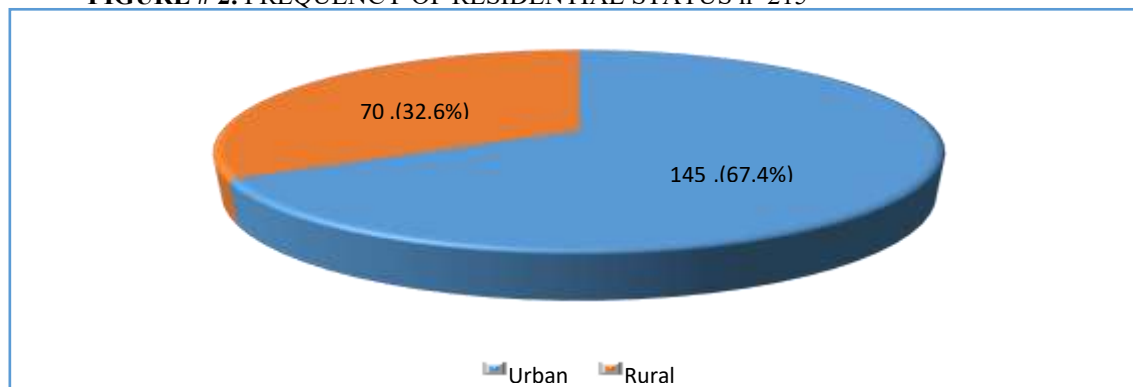
In the gender distribution, 136 (63.3%) were classified as male while 79 (36.7%) were classified as female as shown in **FIGURE 1.**

FIGURE # 1. FREQUENCY OF GENDER n=215



The data reveals that 67.4% of the population were living in urban areas, while 32.6% were residents of rural regions as shown in **FIGURE 2.**

FIGURE # 2. FREQUENCY OF RESIDENTIAL STATUS n=215



In terms of marital status, 49 individuals, representing 22.8% of the total, were single. Meanwhile, 126 individuals, accounting for 58.6% of the total, were married. Additionally, 29 individuals, or 13.5% of the total, were divorced, and 11 individuals, making up 5.1% of the total, were widowed as shown in **TABLE 3**.

TABLE # 3. FREQUENCY OF MARITAL STATUS n=215

MARITAL STATUS	FREQUENCY	PERCENTAGE
Single	49	22.8%
Married	126	58.6%
Divorced	29	13.5%
Widowed	11	5.1%

The ethnic distribution shows that Urdu speakers are the most prevalent, comprising 45.1% of the population. Sindhis follow with 24.2%, while Punjabis make up 20.0%. Balochis account for 7.0%, and Pathans are the smallest group at 3.7% as shown in

TABLE 4.

TABLE # 4. FREQUENCY OF ETHNICITY n=215

ETHNICITY	FREQUENCY	PERCENTAGE
Balochi	15	7.0%
Pathan	8	3.7%
Punjabi	43	20.0%
Sindhi	52	24.2%
Urdu	97	45.1%

The educational status distribution shows that 14.0% of the population has no formal education, 13.5% have completed primary education, 52.6% have secondary education, 11.2% hold intermediate qualifications, and 8.8% are graduates or have higher education as shown in **TABLE 5**.

TABLE # 5. FREQUENCY OF EDUCATIONAL STATUS n=215

EDUCATIONAL STATUS	FREQUENCY	PERCENTAGE
No formal education	30	14.0%
Primary	29	13.5%
Secondary	113	52.6%
Intermediate	24	11.2%
Graduate or above	19	8.8%

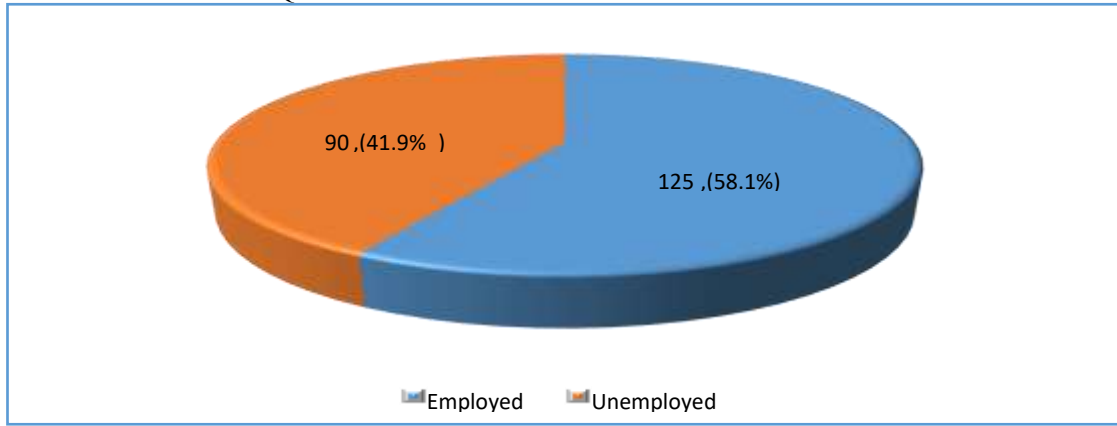
The distribution of substance use shows that opiates are the most frequently used, accounting for 68.8% of the population. This is followed by sedatives, comprising 19.5%, and alcohol, which represents 11.6% of the cases as shown in **TABLE 6**.

TABLE # 6. FREQUENCY FOR TYPE OF SUBSTANCE USE n=215

TYPE OF SUBSTANCE USE	FREQUENCY	PERCENTAGE
Alcohol	25	11.6%
Sedatives	42	19.5%
Opiates	148	68.8%

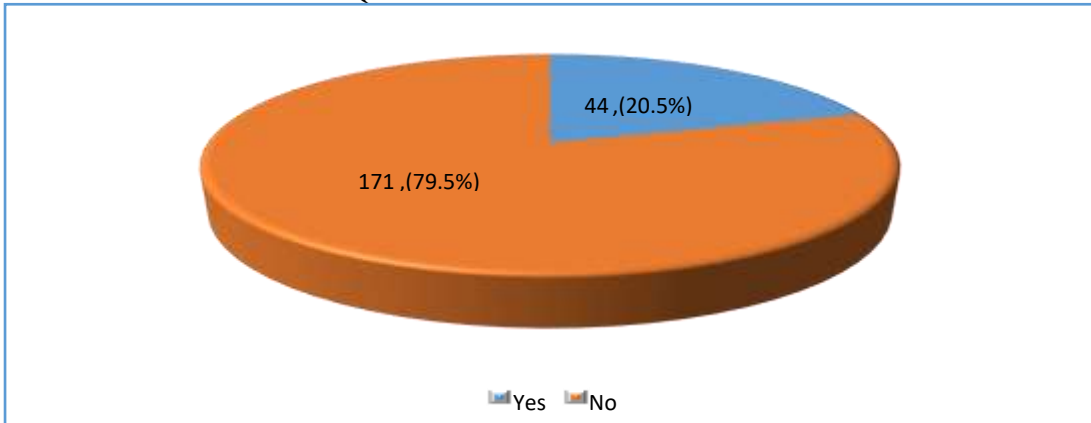
In terms of occupational status, 125 individuals, representing 58.1% of the total, were employed, whereas 90 individuals, accounting for 41.9% of the total, were unemployed as shown in **FIGURE 3**.

FIGURE # 3. FREQUENCY OF OCCUPATIONAL STATUS n=215



Depression was present in 20.5% of the patients, affecting a total of 44 individuals as shown in **FIGURE 4**.

FIGURE # 4. FREQUENCY OF DEPRESSION n=215



Stratification of age group, gender, marital status, monthly income, residential status, and occupational status was done with respect to depression in order to assess statistical difference as shown from **TABLE [7-12]**.

TABLE # 7. STRATIFICATION OF AGE GROUP WITH DEPRESSION n=215

AGE GROUP [years]	DEPRESSION		P-VALUE
	Yes	No	
18 – 40	19 (8.8%)	75 (34.9%)	0.936
>40	25 (11.6%)	96 (44.7%)	

Applied Chi-Square test

TABLE # 8. STRATIFICATION OF GENDER WITH GENDER n=215

GENDER	DEPRESSION		P-VALUE
	Yes	No	
Male	27 (12.6%)	109 (50.7%)	0.770
Female	17 (7.9%)	62 (28.8%)	

Applied Chi-Square test

TABLE # 9. STRATIFICATION OF MARITAL STATUS WITH DEPRESSION n=215

MARITAL STATUS	DEPRESSION		P-VALUE
	Yes	No	

Single	7 (3.3%)	42 (19.5%)	0.402
Married	27 (12.6%)	99 (46.0%)	
Divorced	6 (2.8%)	23 (10.7%)	
Widowed	4 (1.9%)	7 (3.3%)	

Applied Chi-Square test

TABLE # 10. STRATIFICATION OF MONTHLY INCOME WITH DEPRESSION n=215

MONTHLY INCOME	DEPRESSION		P-VALUE
	Yes	No	
18000 – 40000	25 (11.6%)	109 (50.7%)	0.398
>40000	19 (8.8%)	62 (28.8%)	

Applied Chi-Square test

TABLE # 11. STRATIFICATION OF RESIDENTIAL STATUS WITH DEPRESSION n=215

RESIDENTIAL STATUS	DEPRESSION		P-VALUE
	Yes	No	
Urban	27 (12.6%)	118 (54.9%)	0.335
Rural	17 (7.9%)	53 (24.7%)	

Applied Chi-Square test

TABLE # 12. STRATIFICATION OF OCCUPATIONAL STATUS WITH DEPRESSION n=215

OCCUPATIONAL STATUS	DEPRESSION		P-VALUE
	Yes	No	
Employed	27 (12.6%)	98 (45.6%)	0.627
Unemployed	17 (7.9%)	73 (34.0%)	

Applied Chi-Square test

DISCUSSION

Depression is a prevalent and serious mental health condition that can be significantly influenced by the use of central nervous system (CNS) depressants [81]. These substances, which include medications such as benzodiazepines, opioids, and other sedatives, are commonly prescribed for anxiety, pain, and sleep disorders. However, their effects on mood and mental health can be complex and multifaceted. While CNS depressants can provide relief from symptoms of anxiety and pain, they can also contribute to the onset or exacerbation of depressive symptoms [82].

The interplay between CNS depressant use and depression is an area of growing concern. Evidence suggests that the sedative effects of these drugs can worsen mood disorders, leading to increased prevalence of depressive symptoms among users. Moreover, the symptomatology of depression in these patients can vary widely, affecting their overall well-being and quality of life [83]. Understanding the prevalence and specific symptoms of depression in this population is essential for developing targeted treatment strategies and improving patient outcomes.

This study seeks to explore the extent of depressive symptoms among individuals using CNS depressants and to characterize their symptom profiles. By identifying the relationship between CNS depressant use and depression, the research aims to provide insights that could enhance clinical approaches and support better mental health management for affected patients.

The relationship between central nervous system depressant use and depression is complex and multifaceted [84]. This study sheds light on the prevalence and symptomatology of depression among patients using CNS depressants, revealing critical insights that can guide clinical practice and patient management.

Our findings indicate a notable prevalence of depression among individuals using CNS depressants. This aligns with existing literature suggesting that the use of these medications is associated with an increased risk of developing depressive symptoms [85]. The prevalence rates observed in our study are consistent with previous research, which highlights the dual role of CNS depressants: while they are effective for managing symptoms of anxiety, pain, and sleep disorders, they can also contribute to or exacerbate depressive symptoms.

Several factors may explain this association. CNS depressants, particularly benzodiazepines and opioids, can alter neurotransmitter levels and brain function, potentially leading to mood disturbances.

Chronic use of these substances can cause changes in brain chemistry that predispose individuals to depression [86]. Furthermore, the sedative effects of these drugs may mask underlying depressive symptoms or lead to a cycle of worsening mental health.

The symptom profile of depression in patients using CNS depressants appears to be diverse. Common symptoms reported include persistent sadness, lack of motivation, fatigue, and difficulty concentrating [87]. These symptoms are consistent with typical depressive disorders but may be compounded by the effects of CNS depressants. Notably, the impact of these symptoms on daily functioning and quality of life can be significant, affecting both personal and professional aspects of patients' lives.

It is also important to consider the potential interaction between CNS depressants and other medications or substances that patients might be using. Polypharmacy, particularly in individuals with chronic pain or multiple mental health conditions, can further complicate the symptomatology of depression [88]. Drug interactions may amplify depressive symptoms or create new challenges in managing mental health.

The findings of this study have important clinical implications. First, healthcare providers should be vigilant when prescribing CNS depressants, particularly to individuals with a history of depression or those at risk for mental health issues [89]. Comprehensive assessment and ongoing monitoring for depressive symptoms are crucial for managing patients on these medications.

Second, there is a need for integrated treatment approaches that address both the underlying condition being treated and the potential for depressive symptoms. For instance, incorporating psychological therapies, such as cognitive-behavioral therapy (CBT), alongside pharmacological treatment, may offer a more balanced approach to managing both physical and mental health [90]. Additionally, alternative medications or non-pharmacological treatments should be considered for patients who experience significant depressive symptoms as a result of CNS depressant use.

Further research is needed to explore the mechanisms underlying the relationship between CNS depressant use and depression. Longitudinal studies could provide insights into how long-term use of these medications affects mood over time and whether certain types of CNS depressants carry a higher risk of depression compared to others [91]. Additionally, research into individualized treatment strategies that account for the specific needs and risk factors of patients using CNS depressants could enhance clinical outcomes.

This study is not without limitations. The cross-sectional design limits the ability to establish causality between CNS depressant use and depression. Self-reported data on depressive symptoms may also be subject to bias. Future studies should aim to use longitudinal designs and objective measures to validate these findings and provide a more comprehensive understanding of the impact of CNS depressants on mental health.

In our study, depression was documented in 44 (20.5%) of the patients. In another study, the prevalence of depression was found to be 16.8% [1]. The study by Adewuya AO, et al noted the presence of depression in 15% of patients [92]. The prevalence and symptomatology of depression among patients using CNS depressants highlight a critical area of concern in clinical practice. Recognizing the dual impact of these medications on both physical and mental health is essential for effective patient management. By improving our understanding of this relationship, we can better support patients and develop more effective treatment strategies that address both their physical and mental health needs.

CONCLUSION

It is to be concluded that a notable presence of depression among patients, with males being the predominant group affected. Opiates emerged as the most commonly used substance, followed by sedatives and alcohol. These findings emphasize the importance of addressing mental health concerns, particularly depression, in individuals using CNS depressants to improve overall treatment outcomes.

Conflict of Interest: None

Limitations: This is a hospital based study and can't be generalized to general population.

REFERENCES

1. Luitel NP, Baron EC, Kohrt BA, Komproe IH, Jordans MJD. Prevalence and correlates of depression and alcohol use disorder among adults attending primary health care services in Nepal: a cross sectional study. *BMC Health Serv Res.* 2018;18(1).
2. Valenstein M, Kiran Khanujua Taylor M, Austin K, Helen Kales MC, McCarthy JF, Blow FC. Article benzodiazepine use among depressed patients treated in mental health settings [Internet]. Vol. 161, *Am J Psychiatry.* 2004. Available from: <http://ajp.psychiatryonline.org>
3. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet.* 2007;370(9590):851-8.
4. Kader Maideen SF, Mohd. Sidik S, Rampal L, Mukhtar F. Prevalence, associated factors and predictors of depression among adults in the Community of Selangor, Malaysia. *Plos One.* 2014;9(4):e95395.
5. Muhammad Gadit AA, Mugford G. Prevalence of depression among households in three capital cities of Pakistan: need to revise the mental health policy. *Plos One.* 2007;2(2): e209.

6. Poongothai S, Pradeepa R, Ganesan A, Mohan V. Prevalence of depression in a large Urban South Indian population - The Chennai Urban Rural Epidemiology Study (Cures - 70). *Plos One*. 2009;4(9):e7185.
7. Beekman ATF, de Beurs E, van Balkom AJLM, Deeg DJH, van Dyck R, van Tilburg W. Anxiety and depression in later life: co-occurrence and communality of risk factors. *Am J Psychiatry*. 2000;157(1):89-95.
8. Kathryn McHugh R, Weiss RD. Alcohol use disorder and depressive disorders.
9. Goesling J, Henry MJ, Moser SE, Rastogi M, Hassett AL, Clauw DJ, et al. Symptoms of depression are associated with opioid use regardless of pain severity and physical functioning among treatment-seeking patients with chronic pain. *J Pain*. 2015;16(9):84451.
10. Lavie E, Fatseas M, Denis C, Auriacombe M. Benzodiazepine use among opiate-dependent subjects in buprenorphine maintenance treatment: correlates of use, abuse and dependence. *Drug Alcohol Depend*. 2009;99(1-3):338-44.
11. Chen KW, Berger CC, Forde DP, D'Adamo C, Weintraub E, Gandhi D. Benzodiazepine use and misuse among patients in a Methadone Program. *BMC Psychiatry*. 2011;11(1):90.
12. Islam MR, Giasuddin NA, Islam MR. Prevalence of depression and anxiety among patients with substance use disorder and their association with quality of life: a cross-sectional study. *J Addict Res Ther*. 2019;10(381):2.
13. Rayner L, Price A, Evans A. The relationship between depression and prescription opioid misuse in patients with chronic pain: a systematic review and meta-analysis. *J Affect Disord*. 2020;265:495-9.
14. Coupland C, Hill T, Morriss R, Moore M, Arthur A, Hippisley-Cox J. Benzodiazepines, Zdrugs and the risk of depression: real-world data from a longitudinal study. *Int J Geriatr Psychiatry*. 2020;35(2):144-53.
15. Serafini G, Gonda X, Rihmer Z, Amore M. The association between alcohol use disorder and depression in primary care patients: a systematic review and meta-analysis. *Alcohol*. 2021;91:53-61.
16. Moccia L, Pettoruso M, De Crescenzo F, De Risio L, Di Nicola M, Martinotti G, et al. Depression and anxiety symptoms among outpatients with substance use disorders: the role of emotion dysregulation. *Int J Environ Res Public Health*. 2022;19(2):607.
17. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. *N Engl J Med*. 2014;370(23):2219-27.
18. Vallerstnes OM, Jacobsen D, Ekeberg O, Brekke M. Mortality, morbidity and follow-up after acute poisoning by substances of abuse: a prospective observational cohort study. *Scand J Public Health*. 2019;47(4):452-61.
19. Marel C, Sunderland M, Mills KL, Slade T, Teesson M, Chapman C. Conditional probabilities of substance use disorders and associated risk factors: Progression from first use to use disorder on alcohol, cannabis, stimulants, sedatives and opioids. *Drug Alcohol Depend*. 2019;194:136-42.
20. Salik I, Marwaha R. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Sep 21, 2021. Electroconvulsive Therapy.
21. Pleis JR, Lethbridge-Cejku M. Summary health statistics for U.S. adults: National Health Interview Survey, 2006. *Vital Health Stat*. 2007;10(235):7-9.
22. Miller L. Postpartum depression. *JAMA*. 2002;287(6):762-5.
23. Qaseem A, Snow V, Shekelle P, Casey DE Jr, Cross JJ Jr, Owens DK. Evidence-based intervention to improve the palliative care of pain, dyspnea, and depression at the end of life: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2008;148(2):141-6.
24. Roose SP, Glassman AH, Seidman SN. Relationship between depression and other medical illnesses. *JAMA*. 2001;286(14):1687-90.
25. Crystal S, Sambamoorthi U, Walkup JT, Akincigil A. Diagnosis and treatment of depression in the elderly medicare population: predictors, disparities and trends. *J Am Geriatr Soc*. 2003;51(12):1718-28.
26. Unützer J. Clinical practice: late life depression. *N Engl J Med*. 2007;357(22):2269-76.
27. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition/Text Revised. DSM-IV-TR. Washington, DC: American Psychiatric Association; 2000.
28. Singh R, Volner K, Marlowe D. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Jun 20, 2021. Provider Burnout.
29. U.S. Preventive Services Task Force. Screening for depression in adults: a summary of the evidence for the U.S. preventive services task force. *Ann Intern Med*. 2002;136(10): 760-4.
30. Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. *Med Care*. 2003;41(11):1284-92.
31. Mitchell AJ, Chan M, Bhatti H, Halton M, Grassi L, Johansen C, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. *Lancet Oncol* 2011;12:160-74.
32. Horowitz MA, Taylor D. Tapering of SSRI treatment to mitigate withdrawal symptoms. *Lancet Psychiatry*. 2019;6(6):538-46.
33. Saracino RM, Nelson CJ. Identification and treatment of depressive disorders in older adults with cancer. *J Geriatr Oncol*. 2019;10(5):680-4.
34. Knappe S, Einsle F, Rummel-Kluge C, Heinz I, Wieder G, Venz J, et al. Simple guideline-oriented supportive tools in primary care: Effects on adherence to the S3/NV guideline unipolar depression. *Z Psychosom Med Psychother*. 2018;64(3):298-311.

35. Rootes-Murdy K, Carlucci M, Tibbs M, Wachtel LE, Sherman MF, Zandi PP, et al. Nonsuicidal self-injury and electroconvulsive therapy: outcomes in adolescent and young adult populations. *J Affect Disord.* 2019;250:94-8.
36. Tanner J, Zeffiro T, Wyss D, Perron N, Rufer M, Mueller-Pfeiffer C. Psychiatric symptom profiles predict functional impairment. *Front Psychiatry.* 2019;10:37.
37. Knappe S, Einsle F, Rummel-Kluge C, Heinz I, Wieder G, Venz J, et al. Simple guideline-oriented supportive tools in primary care: Effects on adherence to the S3/NV guideline unipolar depression. *Z Psychosom Med Psychother.* 2018;64(3):298-311.
38. Gaynes BN, West SL, Ford CA, Frame P, Klein J, Lohr KN. Screening for suicide risk in adults: a summary of the evidence for the U.S. preventive services task force. *Ann Intern Med.* 2004;18;140(10):822-35.
39. National Center for Injury Prevention and Control. WISQARS (Web-based Injury Statistics Query and Reporting System). <http://webappa.cdc.gov/sasweb/ncipc/mortrate.html> Accessed March 24, 2008.
40. U.S. Preventive Services Task Force. Screening for suicide risk: recommendation and rationale. *Ann Intern Med.* 2004;140(10):820-21.
41. US Food and Drug Administration. Labeling change request letter for antidepressant medications. Rockville, MD; October 28, 2004. <http://www.fda.gov/cder/drug/antidepressants/SSRIlabelChange.htm> Accessed March 24, 2008.
42. Namkung H, Lee BJ, Sawa A. Causal inference on pathophysiological mediators in psychiatry. = Cold Spring Harb Symp Quant Biol. 2018;83:17-23.
43. Maust DT, Solway E, Clark SJ, Kirch M, Singer DC, Malani P. Prescription and nonprescription sleep product use among older adults in the United States. *Am J Geriatr Psychiatry.* 2019;27(1):32-41.
44. Brigo F, Igwe SC, Bragazzi NL, Lattanzi S. Clonazepam monotherapy for treating people with newly diagnosed epilepsy. *Cochrane Database Syst Rev.* 2019;2019(11).
45. Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: Report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Curr.* 2016;16(1): 48-61.
46. The ASAM clinical practice guideline on alcohol withdrawal management. *J Addict Med.* 2020;14(3S Suppl 1):1-72.
47. Qaseem A, Kansagara D, Forcica MA, Cooke M, Denberg TD. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2016;165(2):125-33.
48. Kilpatrick GJ. Remimazolam: non-clinical and clinical profile of a new sedative/anesthetic agent. *Front Pharmacol.* 2021;12:690875.
49. Poisbeau P, Gazzo G, Calvel L. Anxiolytics targeting GABAA receptors: Insights on etifoxine. *World J Biol Psychiatry.* 2018;19(sup1):S36-45.
50. Griffin CE, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects. *Ochsner J.* 2013;13(2):214-23.
51. Wilcock A, Charlesworth S, Twycross R, Waddington A, Worthington O, Murtagh FEM, et al. Prescribing non-opioid drugs in end-stage kidney disease. *J Pain Symptom Manage.* 2017;54(5):776-87.
52. Panchal AR, Bartos JA, Cabañas JG, Donnino MW, Drennan IR, Hirsch KG, et al. Part 3: Adult Basic and Advanced Life Support: 2020 American Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation.* 2020; 142(16_suppl_2):S366-468.
53. Gallo AT, Hulse G. Pharmacological uses of flumazenil in benzodiazepine use disorders: a systematic review of limited data. *J Psychopharmacol.* 2021;35(3):211-20.
54. Lavonas EJ, Akpunonu PD, Arens AM, Babu KM, Cao D, Hoffman RS, et al. 2023 American Heart Association focused update on the management of patients with cardiac arrest or life-threatening toxicity due to poisoning: an update to the American Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation.* 2023;148(16):e149-84.
55. Sneyd JR. Thiopental to desflurane - an anaesthetic journey. Where are we going next? *Br J Anaesth.* 2017;119(suppl_1):i44-52.
56. Ruble JH. The "death" of lethal injection as we know it? The role of chemical execution in the American criminal justice system. *J Pain Palliat Care Pharmacother.* 2014;28(3): 276-81.
57. Haddad SH, Arabi YM. Critical care management of severe traumatic brain injury in adults. *Scand J Trauma Resusc Emerg Med.* 2012;20:12.
58. Majdan M, Mauritz W, Wilbacher I, Brazinova A, Rusnak M, Leitgeb J. Barbiturates use and its effects in patients with severe traumatic brain injury in five European countries. *J Neurotrauma.* 2013;30(1):23-9.
59. Jain P, Aneja S, Cunningham J, Arya R, Sharma S. Treatment of benzodiazepine-resistant status epilepticus: Systematic review and network meta-analyses. *Seizure.* 2022;102:7482.
60. Wood J, Ferguson C. Best evidence topic report. Procedural sedation for cardioversion. *Emerg Med J.* 2006;23(12):932-4.
61. Miner JR, Biros M, Krieg S, Johnson C, Heegaard W, Plummer D. Randomized clinical trial of propofol versus methohexital for procedural sedation during fracture and dislocation reduction in the emergency department. *Acad Emerg Med.* 2003;10(9):931-7.
62. Rodulfo A, Augsten A, Wainwright E, Abramovici G. A case of severe fioricet withdrawal presenting during admission to an inpatient psychiatric unit. *Case Rep Psychiatry.* 2021; 2021:6371953.

63. VanderPluym JH, Halker Singh RB, Urtecho M, Morrow AS, Nayfeh T, Torres Roldan VD, et al. Acute treatments for episodic migraine in adults: a systematic review and metaanalysis. *JAMA*. 2021;325(23):2357-69.
64. Bernstein JE, Ghanchi H, Kashyap S, Podkovik S, Miulli DE, Wacker MR, et al. Pentobarbital coma with therapeutic hypothermia for treatment of refractory intracranial hypertension in traumatic brain injury patients: a single institution experience. *Cureus*. 2020;12(9):e10591.
65. Chau PL. New insights into the molecular mechanisms of general anaesthetics. *Br J Pharmacol*. 2010;161(2):288-307.
66. Löscher W, Rogawski MA. How theories evolved concerning the mechanism of action of barbiturates. *Epilepsia*. 2012;53 Suppl 8:12-25.
67. Cozanitis DA. One hundred years of barbiturates and their saint. *J R Soc Med*. 2004;97(12):594-8.
68. Ho IK, Harris RA. Mechanism of action of barbiturates. *Ann Rev Pharmacol Toxicol*. 1981; 21(1):83-111.
69. Zhang Q, Yu Y, Lu Y, Yue H. Systematic review and meta-analysis of propofol versus barbiturates for controlling refractory status epilepticus. *BMC Neurol*. 2019;19(1):55.
70. Cordato DJ, Herkes GK, Mather LE, Gross AS, Finfer S, Morgan MK. Prolonged thiopentone infusion for neurosurgical emergencies: usefulness of therapeutic drug monitoring. *Anaesth Intensive Care*. 2001;29(4):339-48.
71. Upton RN, Ludbrook GL, Grant C, Doolette DJ. The effect of altered cerebral blood flow on the cerebral kinetics of thiopental and propofol in sheep. *J Am Soc Anesthesiol*. 2000; 93(4):1085-94.
72. Pacifici GM. Clinical pharmacology of phenobarbital in neonates: effects, metabolism and pharmacokinetics. *Curr Pediatr Rev*. 2016;12(1):48-54.
73. Bucove A. Misuse of valuable therapeutic agents: barbiturates, tranquilizers, and amphetamines. *Bull N Y Acad Med*. 1964;40(12):972-9.
74. Roberts DM, Buckley NA. Enhanced elimination in acute barbiturate poisoning - a systematic review. *Clin Toxicol (Phila)*. 2011;49(1):2-12.
75. Rodulfo A, Augsten A, Wainwright E, Abramovici G. A case of severe fioricet withdrawal presenting during admission to an inpatient psychiatric unit. *Case Rep Psychiatry*. 2021; 2021:6371953.
76. Cohen SM, Alexander RS, Holt SR. The spectrum of alcohol use: epidemiology, diagnosis, and treatment. *Med Clin North Am*. 2022;106(1):43-60.
77. Russo CA, Elixhauser A. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs [Internet]. Agency for Healthcare Research and Quality (US); Rockville (MD): May, 2006. Hospitalizations for Alcohol Abuse Disorders, 2003.
78. Alcohol Use Disorder (AUD) in the United States: Age Groups and Demographic Characteristics. <https://www.niaaa.nih.gov/alcohols-effects-health/alcoholtopics/alcohol-facts-and-statistics/alcohol-use-disorder-aud-united-states-age-groupsand-demographic-characteristics>
79. Verhulst B, Neale MC, Kendler KS. The heritability of alcohol use disorders: a metaanalysis of twin and adoption studies. *Psychol Med*. 2015;45(5):1061-72.
80. Sliedrecht W, de Waart R, Witkiewitz K, Roozen HG. Alcohol use disorder relapse factors: a systematic review. *Psychiatry Res*. 2019;278:97-115.
81. Bloor R, Sgouros X. Central nervous system depressants. *Substance Misuse Young People 2019*;pp. 129-62. CRC Press.
82. Jann MW, Slade JH. Antidepressant agents for the treatment of chronic pain and depression. *Pharmacother*. 2007;27(11):1571-87.
83. Zullig KJ, Divin AL. The association between non-medical prescription drug use, depressive symptoms, and suicidality among college students. *Addict Behav*. 2012;37(8): 890-9.
84. Hirschfeld RM. The epidemiology of depression and the evolution of treatment. *Prim Care Compan CNS Disord*. 2012;14:26328.
85. Mossie A, Kindu D, Negash A. Prevalence and severity of depression and its association with substance use in Jimma town, Southwest Ethiopia. *Depress Res Treat*. 2016;2016 (1):3460462.
86. Trivedi MH, Hollander E, Nutt D, Blier P. Clinical evidence and potential neurobiological underpinnings of unresolved symptoms of depression. *J Clin Psychiatry*. 2008;69(2):24658.
87. Garcia ME, Garcia-Morales I, Gil-Nagel A. Prevalence of depressive symptoms and their impact on quality of life in patients with drug-resistant focal epilepsy (IMDYVA study). *Epilepsy Res*. 2015;110:157-65.
88. Nemeroff CB. Prevalence and management of treatment-resistant depression. *J Clin Psychiatry*. 2007;68(8):17.
89. Lambert MV, Robertson MM. Depression in epilepsy: etiology, phenomenology, and treatment. *Epilepsia*. 1999;40:s21-47.
90. DeBattista C. Antidepressant agents. *Basic Clin Pharmacol*. 2018;12.
91. Collett GA, Song K, Jaramillo CA, Potter JS, Finley EP, Pugh MJ. Prevalence of central nervous system polypharmacy and associations with overdose and suicide-related behaviors in Iraq and Afghanistan war veterans in VA care 2010–2011. *Drugs Real World Outcomes*. 2016;3:45-52.
92. Adewuya AO, Oladipo O, Ajomale T, Adewumi T, Momodu O, Olibamoyo O, et al. Epidemiology of depression in primary care: Findings from the Mental Health in Primary Care (MeHPriC) project, Lagos, Nigeria. *Int J Psychiatry Med*. 2022;57(1):6-20.