

## ORIGINAL RESEARCH

# Assessment of memory impairment and its relation with the age of onset and duration of exposure of opioid dependence in Opioid Use Disorder Patients

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### ABSTRACT

**Background:** The Prevalence of current use of any opioid in India is 2.06%. Several studies point to the cognitive impairment in opioid abusers across various cognitive domains which often go undetected. Patients with Opioid Use Disorder, OUD exhibit poorer performance on neuropsychological measures of learning, memory, and visuospatial ability. Early age of onset and prolonged duration of exposure can be an important risk factor of cognitive dysfunction in these patients. **Aims & objectives:** To find out memory impairment in Opioid Use Disorder Patients and its correlation with age of onset and duration of opioid dependence. **Materials & methods:** A cross-sectional study on 40 OUD Patients was carried out from January 2021 to August 2022 with a focus on the prevalence of memory impairment in them. After taking informed written consent their different memory domains were tested using PGI Memory Scale and the results obtained were correlated with the age of onset and duration of opioid dependence. **Results:** In our study 30(75%) subjects had dysfunction present in Verbal retention for dissimilar pairs which was maximum among the other subsets. Considerable number of subjects had dysfunction present in Remote memory also 22 (55%). Minimum dysfunction was found in the recent memory 6(15%). We also found significant correlation between duration of opioid dependence and the mental balance. Other memory subsets failed to show any correlation with the age of onset and duration of opioid dependence. **Conclusion:** Assessment of memory impairment among OUD patients could be possible using PGI Memory Scale. Early intervention and knowledge of cognitive deficits in OUD Patients might help in their better management and expecting improved outcomes. Further more studies are needed to be carried out in the same field.

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### INTRODUCTION

Substance use, irrespective of the type of drug, accounted for 42 million years of healthy life lost [Disability-Adjusted Life Years (DALYs)] across the globe. (1) In 2017, an estimated 271 million people, or 5.5 per cent of the global population aged 15–64, had used drugs in the previous year. (1) Addiction to opioids and opiates has been considered as a major global health problem since the 2000s. (2) Opioid use disorder (OUD) affects over 16 million people worldwide and there are over 120,000 deaths annually

attributed to it. The use of non-prescribed opioids is on the rise in Asia. (3) About 0.7% of Indians (approximately 77 lakh individuals) are estimated to be affected with opioid use problems. (4) Although the prevalence of people injecting illicit drugs in India is low relative to West with an estimate between 0.18 and 1.1 million. The rapid growth in the population of injection drug users poses new challenges in the management and care of these patients. (5) Opioids cause respiratory depression and death from opiate poisoning is nearly always due to respiratory

arrest or obstruction. They cause direct stimulation of the chemo trigger zone for emesis.(6) Though primarily used for analgesia opioids are also found to be associated with hyperalgesia.(7) Many develop constipation and altered bowel function.(8) These inhibit esophageal sphincter relaxation and reduce gastric hydrochloric acid secretion.(9,10) They are modestly immunosuppressive and increased susceptibility to infection and tumor spread have been reported.(11)

Several studies point to the cognitive impairment in opioid abusers across various cognitive domains. Patients with OUD exhibit deficits in inhibition, planning, and problem-solving. Patients with OUD also exhibit poorer performance on neuropsychological measures of learning, memory, and visuospatial ability.(12,13) Patients with OUD scored poorer in verbal memory tests including immediate recall. Also when controlled for age and education, a significant correlation was seen between digit backward test, DBT score and the duration of opium use and opium use quantity. Even their digit symbol substitution test, DSSST score was associated with the duration of opium use.(14) Bruhn and Maage compared marijuana/amphetamine/hallucinogen plus opioid and no significant difference was noticed but no information was presented about the amount and duration of opioid use, which might have had significant effects on the extent of cognitive deficits.(15) Darke et al. found that methadone-maintained heroin patients performed more poorly on all neuropsychological domains. Also they noted that the methadone group had high rates of polysubstance use, overdose, head injury and comorbid psychopathology and found that the neuropsychological deficits identified were more characteristic of those with associated comorbidities, further raising issues regarding the specificity of findings reported.(16) Impairment ranging from 23% in orientation to 96% in delayed recall among patients was seen in another study. Most common affected domains among total cases and tramadol-alone abuse patients were memory (delayed recall), visuospatial processing, and language.(17) Prolonged use of opiates, such as heroin, is associated with a deleterious effect on intellectual functioning.(18) In a study abstinent abusers performed better than the methadone group on a measure of word memory (Recognition Memory). No correlation of either the duration or intensity of opiate use with the degree of cognitive testing deficits on any of the studied measures.(19)

Though we observed various studies showing the affect of substance abuse on cognitive functioning but only a few of them are seen elucidating the effect of opioids exclusively in the context of memory impairment and how has it been related to their age of onset and duration of opioid dependence. Considering all these lacunae present in existing literature we planned to carry out a study among opioid use

disorder patients and we aimed to look for cognitive impairment in opioid use disorder patients with the help of PGI Memory Scale taken from PGI Battery of Brain Dysfunction.

## MATERIAL AND METHODOLOGY

A descriptive observational cross sectional study was carried out in the Department of Physiology and in association with the Department of Psychiatry in L.H.M.C. and S.S.K.H., New Delhi. The study period was from January 2021 to August 2022. Adult Patients (18 – 45 years) of either gender diagnosed as a clinical cases of opioid use disorder by treating psychiatric physician. All 40 study participants were free from withdrawal symptoms of opioid abuse and were maintained on buprenorphine treatment. Potential subjects were excluded if they had history of neurological disease or any psychiatric illness before onset of opioid dependence; any intellectual disability or mental retardation because of congenital diseases or any other major illness; Patient with history of chronic substance abuse except opiates and smoking. After ethics clearance we started recruiting patients. Patients coming to psychiatry department and diagnosed by the psychiatrist as clinical cases of opioid use disorder, based on DSM 5 were recruited for the study and consent was taken for our study participation. After obtaining informed written consent, the detailed history and clinical examination, was done following with their memory assessment with the help of PGI Memory Scale.

## PGI MEMORY SCALE

It defines memory as the ability to retain and produce impressions once perceived intentionally. Includes verbal and non-verbal material and measures remote, recent, immediate, short term, very short term, intermediate term, and long term memory. Correlation of PGI memory scale with Boston's Memory scale and Wechsler's memory scale were found to be .71 and .85 respectively. It has 10 subsets: Remote memory, Recent memory, Mental balance, Attention concentration, Delayed recall, Immediate recall, Verbal retention for similar pairs, Verbal retention for dissimilar pairs, Visual retention, Recognition. (20)

## RESULTS

We carried out a descriptive cross sectional observational study in our hospital, Lady Hardinge Medical College, where in we recruited 40 diagnosed opioid use disorder patients. All the parameters used in the study were checked for the normality and then appropriate parametric / non parametric tests were applied.

The basic demographic and clinical profile of the opioid use disorder patients. (n=40) is shown in table 1. The mean age of the study group was  $26.43 \pm 5.5$  yrs and age distribution of subjects varies from 19 years (minimum) to 44 years (maximum). The age of onset of opioid dependence was seen ranging

from 12 years to 37 years with a mean  $\pm$  SD of  $21.53 \pm 5.344$ . The duration of opioid dependence ranges from 1 to 11 years with a mean period of  $4.9 \pm 1.98$  yrs. Among the total 40 participants 75% were having normal BMI (n=30). 20% of the OUD patients of our study were underweight (n=8) and 1 participant each in the category of overweight and obesity were found in the study. Among these OUD Patients 32.5% subjects come from the lower middle group, 52.5% from the upper lower group and remaining 15% from the lower group. (Table 2.) Of all the 40 subjects 70% were educated till primary school, 17.5% till middle school and only 12.5% were high school pass (n=28, 7 and 5 respectively) and none had education beyond high school. (Table 2)

Analysis of cognitive dysfunction in different memory domains among opioid use disorder patient (n=40) based on PGI memory scale has been shown in table 3 and fig 1. 22(55%) subjects had dysfunction in

Remote memory, 6(15%) in Recent memory, 13(32.5%) in mental balance, 17(42.5%) in Attention and Concentration domain, 23(57.5%) in Delayed recall, 16(40%) in Immediate recall, 24(60%) in Verbal retention for similar pairs, 30(75%) in Verbal retention for dissimilar pairs, 13(32.5) in visual retention, and 8(20%) subjects had dysfunction in recognition domain of memory. Maximum number of subjects had dysfunction in the verbal retention for dissimilar pairs whereas least number of subjects in our study were affected on recent memory domain.

Correlation of different subsets of the PGI Memory Scale with the age of onset and duration of opioid dependence in opioid use disorder patients is depicted in table 4. Correlation of mental balance with the duration of opioid dependence was found significant with a p value of 0.0311, whereas all other correlations were found not significant.

**Table 1: Presents the basic demographic profile and clinical profile of the study subjects.**

	Mean	S.D.
Age (years)	26.43	5.500
Age of onset of opioid dependence (years)	21.28	5.364
Duration of opioid dependence (years)	4.9	1.985
Height (cm)	170.5	7.497
Weight (kg)	58.83	8.199
BMI ( kg/m <sup>2</sup> )	20.19	2.248

**Table 2: Distribution of number of subjects among different socioeconomic classes. (n = 40)**

Body mass index	No. of Subjects	
Body mass index	Underweight	8(20%)
	Normal	30(75%)
	Overweight	1(2.5%)
	Obese	1(2.5%)
Kuppuswamy socioeconomic status	Class 3 (lower middle)	13(32.5%)
	Class 4 (upper lower)	21(52.5%)
	Class 5 (lower)	6(15%)
Educational qualification	Primary school	28(70%)
	Middle school	7(17.5%)
	High school	5(12.5%)

**Table 3: Cognitive dysfunction in different memory domains among opioid use disorder patient based on PGI memory scale. (n=40)**

PGIMS SUBSETS	Normal (no. of subjects)	Dysfunction present (No. of subjects)	
		DR = 2	DR = 3
Remote Memory	18(45%)	18(45%)	4(10%)
Recent Memory	34(85%)	5(12.5%)	1(2.5%)
Mental Balance	27(67.5%)	10(25%)	3(7.5%)
Attention And Concentration	23(57.5%)	11(27.5%)	6(15%)
Delayed Recall	17(42%)	17(42%)	6(15%)
Immediate Recall	24(60%)	9(22.5%)	7(17.5%)

Verbal Retention for Similar pairs	16(40%)	21(52.5%)	3(7.5%)
Verbal Retention for Dissimilar pairs	10(25%)	11(27.5%)	19(47.5%)
Visual Retention	27(67.5%)	7(17.5%)	6(15%)
Recognition	32(80%)	7(17.5%)	1(2.5%)

DR – dysfunction rating.

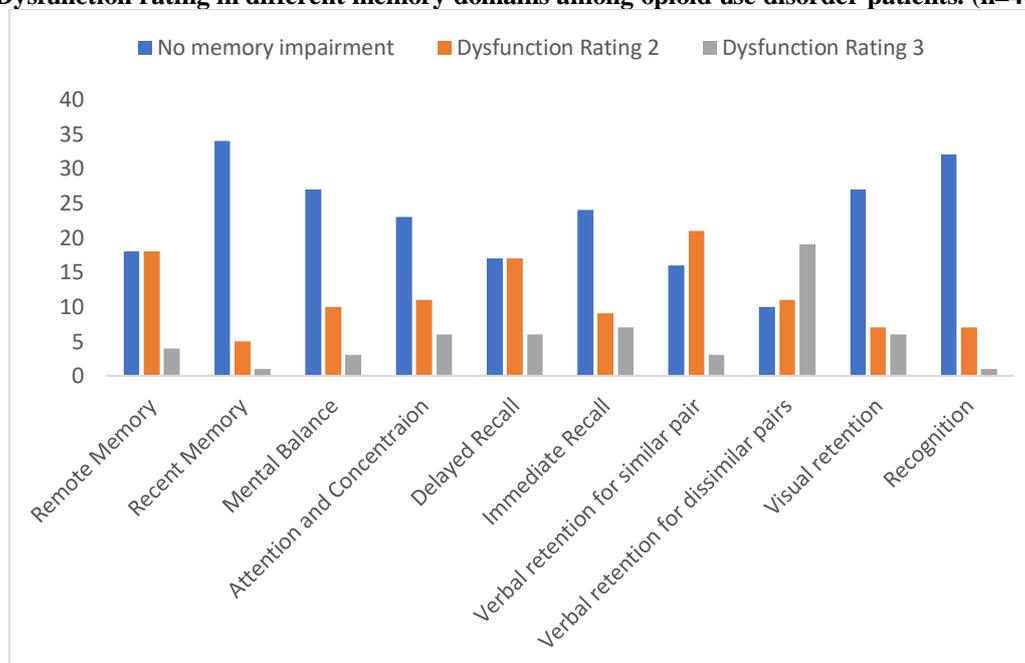
**Table 4: Correlation of PGI memory scale with age of onset and duration of opioid dependence in opioid use disorder patients (n=40)**

PGIMS SUBSETS	Age of onset of opioid dependence		Duration of opioid dependence	
	r	P	r	P
Remote Memory	0.0660	0.6858	0.2185	0.1755
Recent Memory	0.0328	0.8407	0.0290	0.8586
Mental Balance	0.0463	0.7765	0.3414	0.0311*
Attention And Concentration	0.0690	0.6721	0.0773	0.6352
Delayed Recall	0.0325	0.8419	0.2026	0.2100
Immediate Recall	0.0790	0.6277	0.0390	0.8110
Verbal Retention for Similar pairs	0.1408	0.3862	0.0905	0.5785
Verbal Retention for Dissimilar pairs	0.1353	0.4050	0.0564	0.7295
Visual Retention	0.0988	0.5442	0.0157	0.9233
Recognition	0.1810	0.2700	0.0869	0.5988

p > 0.05 - Not Significant (NS), p < 0.05 – Significant\*

p < 0.01 - Highly Significant\*\*, p < 0.001- Very Highly Significant\*\*\*

**Fig 1: Dysfunction rating in different memory domains among opioid use disorder patients. (n=40)**



## DISCUSSION

We assessed memory impairment in opioid use disorder patients and also we looked for its correlation with the age of onset and duration of opioid dependence among these patients.

Of all 40 patients, 39 were male and one was female patient. This is in accordance with the more

prevalence of substance abuse in males in Indian context. Similar to ours, in a North Indian study by Bhat A et al conducted at deaddiction centre of a tertiary care hospital 97.5% opioid patients were male population.(5) Age of the opioid use disorder patients in our study ranged from 19 to 44 years with a mean of  $26.43 \pm 5.50$  yrs. Majority of the subjects were in

their 20s, and similar distribution was seen in the study by Bhat A et al where in 54.05% patients belonged to 20-29 age group.(5) Age of onset of opioid dependence ranged from 12 to 37 years with a mean of  $21.28 \pm 5.364$  yrs. Duration of opioid dependence ranged from 1 to 11 yrs with a mean of  $4.9 \pm 1.985$  yrs. Our study group had a mean BMI of  $20.19 \pm 2.248$ . 30 out of 40 (75%) had normal BMI, 8 subjects (20%) were underweight and 1 participant each in the category of overweight and obese.

Based upon Kuppaswamy SES Socioeconomic assessment 32.5% subjects were from lower middle group, 52.5% from the upper lower group and 15% belonged to the lower socioeconomic group. While study by Bhat A et al study had 37.84% patients coming from upper middle, 48.65 from lower middle and lower socioeconomic group comprised 10%. None of the study participants had education beyond high school. 70% had attained primary education, 17.5% till middle school and only 12.5% were high school pass.

PGI memory scale is a popular and reliable test for assessing memory considering the educational and socioeconomic background of Indian population. In our study 30 (75%) subjects had dysfunction present in Verbal retention for dissimilar pairs which was maximum among the other subsets. Considerable number of subjects had dysfunction present in Remote memory also 22 (55%). Minimum dysfunction was found in the recent memory 6 (15%). Unlike our finding Kumar C R et al found in their study 86.67% substance abuse patients having recent memory dysfunction and 80% having immediate recall dysfunction. But similar to our study they also found dysfunction in verbal retention in 66.66% substance dependent patients.(21)

There are multiple studies pointing out changes in brain parenchyma among opioid abusers. Differences in both grey and white matter have been reported in OUD patients when compared with healthy controls. This may be the reason for the cognitive dysfunctioning and memory impairments seen in these patients.(22) Individuals maintained on long-term opioid agonist treatment have shown enlargement in the right caudate nucleus where as reduced volume in the right amygdala, anterior cingulate cortex and orbitofrontal cortex. Also these changes were found to be more in those with longer duration of OUD.(23) A meta-analysis of neuroimaging studies reported atrophy of the fronto-temporal region, including the superior and inferior frontal gyrus, superotemporalgyrus, orbitofrontal gyuras well as insula in the opioid-dependent individuals.(12) Also decreased gray matter density was appreciated in bilateral insula, bilateral superior temporal cortex, right uncus, and left fusiform cortex.(24)

Significant damage to white matter is also seen in OUD in several areas. A meta-analysis reported significant reductions in fractional anisotropy in the

bilateral frontal subgyral regions extending from the limbic structures to the prefrontal cortex.(25) These changes have been hypothesized as secondary to degradation of myelin sheath through alteration of myelin-specific genes, mitochondrial dysfunction and neuronal apoptosis.(26)

Neuroimaging, also has showed significantly compromised white matter bilaterally in the frontal lobes. Reductions in dopamine D2 receptor density in the striatum have been reported in users of opiates and methamphetamine.(27,28) In methamphetamine users, reduced D2 binding in the striatum was associated with reduced metabolic activity in the orbitofrontal cortex (OFC).(28) Functional magnetic resonance imaging (fMRI) studies of methamphetamine users revealed reduced brain activation in orbitofrontal and dorsolateral prefrontal areas when compared with controls.(29)

We also found significant correlation between duration of exposure of the drug and the mental balance. This result is supported by Martinez A R et al and Moghaddam S H et al who also found that increased duration of drug dependence increases the risk of cognitive dysfunction.(30) Also in another study by Wollman SC et al regression analysis have shown negative association of grey matter changes with opioid use duration and length of abstinence.(12) We found no other significant association between duration of opioid dependence and other memory domains. The reason for this could be a shorter time span (Mean  $\pm$  SD of  $4.9 \pm 1.985$  years) of opioid dependence among our study group. When correlated for age of onset no significant association was noticed with any of the memory impairment and this could be attributed to the mean age of onset in our study population which was  $21.28 \pm 5.364$  yrs, and major structural and functional development of human brain is completed by then.

Further study on a larger sample size is recommended. A study taking into consideration the form and dosage of opioids and their distinct effect on cognition should be done. More Studies should be conducted to assess the effect of several other factors on cognition in OUD patients.

## CONCLUSIONS

We carried out this study among 40 OUD patients with the aim of assessing their memory impairment. Assessment of memory impairment among OUD patients could be possible using PGI Memory Scale. Knowledge of memory impairment and its correlation with the age of onset and duration of opioid dependence emphasizes the need for early intervention which would possibly ensue speedy recovery of these patients. Better memory will help in keeping better compliance with the ongoing treatment and improve the functioning in the daily living activities of OUD Patients. Overall it could open the gates for their better prognostic outcomes.

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