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Research Paper

Clinical Profile and Psycho-Social Consequences of the People

with Alcohol and Opioid Dependence during COVID-19

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ABSTRACT

Background: COVID-19 and resulting lockdown both are impacted in different aspect of psychosocial of the human life. **Aims:** This article aims to study the clinical profile and psycho-social consequences in COVID-19 pandemic on people with alcohol and opioid dependence. **Methods:** The self-developed semi-structured Questionnaire, for assessing the factors which were problematic situation for patient during lockdown was specially designed for the study. The collected Data was analyzed with the help of SPSS 16 version. Descriptive statistics including mean and standard deviation was used to describe the characteristics of the study. **Result and Conclusion:** Due to lockdown most of people have lost his earning resource and people with substance abuse leads to relapse and resulting use of multiple substance, that can be cause severe health complications like withdrawal and multiple psychological problems which is directly impacted on whole family, these conditions are making them prone to procure drugs in illegal way.

Keywords: COVID-19, Lockdown, Social, Psychological, consequences.

Gorona virus disease, one of the most highly infectious diseases was reported worldwide as pandemic. The primary measures contain the outbreak, like home quarantine and continuous lockdown are eventually leading to insurmountable economic burden at community level and are forcing the mass to face various unwanted emotional reaction, psychological complications, behavioral changes including excessive substance abuse, and another part those people who are suffering from substance use disorder and belong to the marginalized community and are invariably more prone to contract infection during the COVID-19 pandemic (Dubey et al 2020). Lockdown restrictions have undoubtedly impacted the majority of the general population; they may have disproportionately affected vulnerable populations, such as people who use drugs, many of whom rely heavily on health and social services. People who use drug (PWUD) also suffer from a higher prevalence of mental health issues compared to the general population, which may be further compounded by the self-isolation that COVID-19 has necessitated and the inability of critical services to address PWUD's needs during the

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pandemic. For instance, early reports have shown negative social and psychological effects from COVID-19, which have been associated with increased risk of relapse and drug consumption among PWUD (Russell et al 2020). Persistent use of psychoactive substances increases risk of substance use disorders (SUDs) bio-psychosocial disorders with multiple risk factors interacting at individual and contextual levels resulting in co-morbid health conditions and affecting people formal social and economic backgrounds. The health consequences of SUDs (e.g., cardiovascular diseases, respiratory diseases, immune and central nervous system depression, and psychiatric disorders) and the associated environmental challenges (e.g., housing instability, unemployment, and criminal justice involvement) increase risk for COVID-19. COVID-19 adds to the complexity of SUD as it affects the lives of individuals with SUD.

It has found that increases in anxiety, depression, and stress in response to the COVID-19 (Pfefferbaum et al 2020), individuals may similarly use substances to cope with the increased negative affect in response to the pandemic COVID -19. These maladaptive coping mechanisms sit in the larger context of COVID-19 social distancing and "stav-athome" measures; factors that may limit opportunity for healthier emotion regulation strategies, including social interaction, physical activity, and opportunities for behavioral activation (e.g., exercise with friends at parks and playground). It is possible that increased COVID-19-associated worry and fear may contribute to substance use initiation, but research has not examined how individual differences in such psychological factors may differ between those who used substances before COVID-19, those who began using substances after the COVID-19 outbreak, and those who do not use substances. Further, as suggested by negative reinforcement models of substance use (Gareyet al 2020) using substances to cope with increased negative emotion (i.e., coping motives) may be specifically related to the initiation and maintenance of substance use problems (Hussong et al 2011). There is concern the Coronavirus Disease (COVID)-19 pandemic is having a negative impact on the mental health of the general population through a range of suggested mechanisms: fear, uncertainty, and anxiety; social distancing/isolation; loneliness; and economic repercussions (Gunnell et al 2020). Previous disasters such as the severe acute respiratory syndrome in 2003 (Chan et al 2006) contributed to increased anxiety, mood, and thought disorders, adjustment disorders, and post-traumatic stress disorders (PTSD (Courtet et al 2020), resulting, in extreme cases, in suicidal behaviours (e.g., suicidal ideation, suicide attempts, and actual suicide) (Mamun et al 2020) especially in cases of concomitant Substance Use Disorder (SUD). A recent study from the Well Being Trust the high levels of stress, isolation and unemployment due to the COVID-19 pandemic could cause up to 75,000 "deaths of despair" related to deaths to drug, alcohol, and suicide (Petterson et al). Evidence suggested that lower mental health quality, elevated anxiety and depression and posttraumatic stress disorder (PTSD) in individuals who have recovered from acute COVID-19. In a recent US cohort analysis, close to one in five (18.1%) COVID-19 survivors were found to have received a psychiatric diagnosis within 3 months of their COVID-19 diagnosis, including 5.8% that were new-onset conditions. Indeed, the risk of being newly diagnosed with a psychiatric disorder was more than twice that of other health events. Early recognition and intervention are crucial to ensure we do not have a significant increase in the number of people experiencing mental health problems, making them vulnerable to other poor health outcomes including substance use disorders. (Wildwing et al 2021, Taquet et al 2020, Méndez et al 2021)

Objective

- To study the Socio-demographic profile of the patients before COVID-19 lockdown, during lockdown, and post-lockdown
- To study the clinical profile in COVID-19 pandemic on people with alcohol and opioid dependence
- To study the social and psychological consequences in COVID-19 pandemic on people with alcohol and opioid dependence

METHODOLOGY

Place & Design of the study

The study has been conducted at State Drug Dependence& treatment centre (SDDTC), Institute of Mental Health, Pt. Bhagwat Dayal Sharma, University of Health Sciences, Rohtak, Haryana. Mixed method research design (Retrospective and Prospective). was used. Purposive sampling technique was used for data collection

Sample

Total sample size 82 was taken from State drug dependence and treatment center in three phases. 30 sample was taken from case record file of pre-lockdown, 22 sample was taken from case record file of during – lockdown and 30 sample was taken from OPD in post-lockdown.

Tools

- **i.** The Sociodemographic data sheet specially designed for the study was used. It includes various sociodemographic variable like age in years, educational qualification, occupation, marital status, current living condition etc.
- Self-developed questionnaire: Latest information from WHO on where COVID-19 ii. is spreading Advice and guidance from WHO on COVID-19. Case record file was used which has been specially designed at state drug deaddiction & treatment centre, Rohtak Haryana. Clinical datasheet of this file was used for assessing Diagnosis, past psychiatric and medical history, family history of substance abuse. Psychological consequences like. Irritability, aggressive behaviour, Restlessness, reduce sleep, reduce appetite, low mood, Anxiety, craving of the patient was also elicit from this file. The impact questionnaire was taken from latest information from WHO on where COVID-19 is spreading and Advice and guidance from WHO on COVID-19. This questionnaire includes- Registration Details, Personal details, Sociodemographic profile, Consequences, Types of substance & taking duration, past history, Family history, Diagnosis, Factors affected to take treatment -What was your first thought when the lock down was announced? What problem you occurred to take substance? Which physical / mental problems occurred when you not find substance? How covid-19 is affecting your addiction / treatment? Which was the most troublesome part of the lock-down restrictions and why? What caused you trouble when you came hospital for treatment during Covid-19?

Procedure

The study has been conducted on the patient's taking treatment from SDDTC. There are 30 participants has been selected retrospectively from 1 Jan 2020 - 22 march 2020 (Prelockdown), and 22 participants has been selected from 24 march 2020 - 30 may 2020 (During lockdown), relevant socio-demographic and clinical data have been collected from case record file and 30 participants has been selected prospectively, from the SDDTC OPD

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after October to November 2020 (Post-lockdown) relevant socio-demographic and clinical data has been collected from patients. Participants fulfilling the study criteria and willing to participate has been approached. Written informed consent has been taken before the data collection. Participant who has not match study criteria or not willing for written consent has been excluded. The Sociodemographic data sheet specially designed for the study and "Self-developed questionnaire" was used to collect data.

RESULT

Table 1 Socio-demographic profile of the patients before COVID-19 lockdown, during lockdown, and post-lockdown

Variables		Pre- lockdown	Du	ring- kdown	Post-			
		N = 30	N =	= 22	N = 30	x2	df	Р
		N (%)	N (~	N (%)		~~	-
Marital status	Married	15 (50%)	10	(45.5%)	21 (70.0%)		4	.328
	Unmarried	14 (46.7%)	10	(45.5%)	8 (26.7%)	4.627		
	Separated	1 (3.3%)	2 (9	9.1%)	1 (3.3%)			
	5 th	0 (0%)	2 (9	9.1%)	2 (6.7%)		10	.358
Marital status Education Employment	8 th	5 (16.7%)	2 (9	9.1%)	6 (20.0%)			
Education	10 th	14 (46.7%)	7 (3	31.8%)	13 (43.3%)]		
Education	12 th	2 (6.7%)	0 (0)%)	3 (10.0%)	10.999		
	Graduate	7 (23.3%)	9 (4	40.9%)	6 (20.0%)			
	Post graduate	2 (6.7%)	2 (9	9.1%)	0 (0%)			
Employment	Student	5 (16.7)	4 (1	18.2%)	2 (6.7%)	_	8	.415
	Self Employed	6 (20.0%)	6 (2	27.3%)	11 (36.7%)			
	Employed	5 (16.7%)	6 (2	27.3%)	8 (26.7%)	0.100		
	Part time employed	3 (10.0%)	3 (1	13.6%)	1 (3.3%)	8.192		
	Unemployed	11 (36.7%)	3 (1	13.6%)	8 (26.7%)			
Current living condition	Joint family	16(53.3%)	4(63.6%) 11		11(36.7%)			
	Nuclear family	14(46.7%)	8(3	6.4%)	19(63.3%)	3.903	2	.142
Age		31.06 <u>+</u> 1.05 29.50 <u>+</u> 7		7.57 33.03 ± 1.12				
Family monthly income		17250 <u>+</u> 11640	50 <u>+</u> 11640.3 15227.3 <u>+</u>		<u>+ 5768.81 12316.7 + 6556.6</u>		6.67	

Table.1 shows socio-demographic variables in pre-lockdown, during lock-down and post-lockdown, all participants were male.

Pre-lockdown- Mean age of participant is 31.06 ± 1.05 and most of them were married 50% followed by 46.7 % unmarried and 3.3% separated, higher level of education was 10^{th} (46%) followed by graduate 23.3%, regarding employment higher no. of participant were unemployed 36.7% followed by self- employed 20%, employed and student were seen equally. Regarding family income 16.7%, most of participant belonging to joint family 53.3% followed by 46.7% from nuclear family with the mean and SD of family income 17250 \pm 11640.3.

During-lockdown- Mean age of participant is 29.50 + 7.57 and Equal no. of participant of married and unmarried (45.5%) and 9.1% were separated, higher level of education were graduate 40.9% followed by10th 31.8%, and in employment, no. of employed and self - employed both were equal (27.3%) followed by student 18.2%, participant belonging to 63.6% from joint family followed by 36.4% from nuclear family with the mean and SD of family income 15227.3 \pm 5768.81.

Post-lockdown - Mean age of participant is 33.03 ± 1.12 and most of them were married 70% followed by 26.7 % unmarried and 3.3% separated, Education: - most of them were educated up to $10^{th}(43.3\%)$ followed by graduate and 8^{th} were equal(20%), in employment higher no. of participant were self-employed 36.7% followed by employed and unemployed 26.7%, participant belonging to 63.3% from nuclear family and 36.7% from join family with the mean and SD of family income 12316.7 \pm 6556.67.

		Pre-	During-	Post-			
Variables		lockdown	lockdown	lockdown			
		N = 30	N = 22	N = 30	x2	Df	Р
		N (%)	N (%)	N (%)			
Physical	Yes	4(13.3%)	0(0%)	23(76.7%)	42 002	2	000
Consequences	No	26(86.7%)	22(100%)	7(23.3%)	42.005	2	.000
Social Consequences	IPR with parent	0(0%)	0(0%)	2(6.7%)		6	.363
	IPR with spouse	3(10.0%)	3(13.6%)	4(13.3%)	6.568		
	High noise level in family	18(60.0%)	14(63.6%)	12(40.0%)			
	None	9(30.0%)	5(22.7%)	12(40.0%)			
Legal	Yes	3(10%)	6(27.3%)	7(23.3%)	2.851	2	.240
Consequences	No	27(90.0%)	16(72.7%)	23(76.7%)			
Occupational Consequences	Inability	0(0%)	0(0%)	5(16.7%)		8	.000
	Jobless	10(33.3%)	4(18.2%)	3(10%)			
	Absent	19(63.3%)	17(77.3%)	10(33.3%)	32.293		
	Suspend	0(0%)	0(0%)	2(6.7%)			
	No	1 (3.3%)	1 (4.5%)	1 (3.3%)			
Other	Yes	2(6.7%)	6(27.3%)	16(53.3%)	15 927		000
consequences	No	28(93.3%)	16(72.7%)	14(46.7%)	15.83/ 2		.000

Table 2. social consequences of patients before COVID-19 lockdown, during lockdown, and Post-lockdown

Variables		Pre- lockdown N = 30 N (%)	During- lockdown N = 22 N (%)	Post- lockdown N = 30 N (%)	x2	Df	Р
Diagnosis	ADS	15(50.0%)	8(36.4%)	15(50.0%)	1.204	2	.548
	ODS	15(50.0%)	14(63.6%)	15(50.0%)			
Other substances	Yes	29(96.7%)	20(90.0%)	22(73.3%)	7.515	2	.023
use	No	1(3.3%)	2(9.1%)	8(26.7%)			
Psychiatric Past illness	Yes	2(6.7%)	2(9.1%)	4(13.3%)	.772	2	.680
	No	28(93.3%)	20(90.9%)	26(86.7%)			
Medical Past	Yes	4(13.3%)	1(4.5%)	2(6.7%)	1.467	2	.480
illness	No	26(86.7%)	21(95.5%)	28(93.3%)			
Family history of	Yes	5(16.7%)	8(36.4%)	11(36.7%)	2 620	2	162
substance use	No	25(83.3%)	14(63.6%)	19(63.3%)	3.029	2	.105

Table 2. 1 Clinical profile of patients before COVID-19 lockdown, during lockdown, and post-lockdown

Table.2.1 shows clinical profile of participants in pre-lockdown, during lock-down and post-lockdown,

In pre-lockdown 50% diagnosed with Alcohol dependence syndrome and 50% diagnosed with Opioid Dependence Syndrome. For all participant with other substance use like (tobacco, cannabinoids) were 96.7%, 13.3% felt physical problem (tremors, body aches, stomach cramps). Social consequences 60% participant suffered with high noise level in the family followed by 10% Interpersonal relationship problem with wife. Only 10% participant faced legal problem (case for fight, drug trafficking). Occupational consequences 63.3% reported absenteeism from his job followed by 33% were jobless and 6.7% reported other type of consequences (debt, stealing, plunder). 6.7% participant already suffering from psychiatric illness (depressive symptom, hallucination,) and 13.3% with medical illness (injury, tuberculosis) followed by 16.7% having family history of substance abuse (tobacco, alcohol).

During-lockdown 36.4% diagnosed with Alcohol dependence syndrome and 63.6% diagnosed with Opioid Dependence Syndrome for all participant with other substance use in 90% of participant, in social consequences 63.6% participant suffered with high noise level in the family followed by 13.6% IPR with wife. Only 27.3% participant faced legal problem and in occupational consequences 77.3% reported absenteeism from his job followed by 18.2% were jobless and 27.3% reported other type of consequences. 9.1% participant already suffering from psychiatric illness and 4.5% with medical illness followed by 36.4% having family history of substance abuse.

Post-lockdown 50% diagnosed with Alcohol dependence syndrome and 50% diagnosed with Opioid Dependence Syndrome for all participant with other substance use in 73.3% of participant, 76.7% felt physical problem and in social consequences 40% participant suffered with high noise level in the family followed by 13.3% IPR with wife. Only 23.3% participant faced legal problem and in occupational consequences 33.3% reported absenteeism from his job followed by 16.7% were in-able to perform his duty and 53.3 % reported other type of consequences. 13.3% participant already suffering from psychiatric illness and 6.7 % with medical illness followed by 36.7% having family history of substance abuse.

Domain	Pre-lockdown	During-lockdown	Post-lockdown	Total
	N=30 (%)	N=22 (%)	N=30 (%)	N=82 (%)
Irritability	25 (83.33%)	13 (59.1%)	24 (80%)	62 (75.6%)
Aggressive	6 (20%)	4 (18.18%)	13 (43.3%)	23 (28.04)
behavior				
Restlessness	17 (56.6%)	11 (50%)	12 (40%)	40 (48.78%)
Reduce sleep	2 (6.6%)	7 (31.81%)	9 (30%)	18 (21.95%)
Reduce appetite	1 (3.3%)	0 (0%)	3 (10%)	4 (4.87%)
Low mood	1 (3.3%)	0 (0%)	5 (16.6%)	6 (7.31%)
Anxiety	1 (3.3%)	8 (36.36%)	2 (6.6%)	11 (13.41%)
Craving	0 (0%)	0 (0%)	3 (10%)	3 (3.65%)

Table 2.2 comparing psychological problem of patients before COVID-19 lockdown, during lockdown, and Post-lockdown

Table. 2.2 shows types of psychological problems of participants in pre-lockdown, during lock-down and post-lockdown, in pre-lockdown highly faced problem is irritability in 83.33% participant and restlessness in 56.6% followed by aggressive behavior in 20% reduce sleep in 2.2% and equal no. 3.3% of participant faced reduce appetite, low mood, anxiety. In during lockdown highly faced problem is also irritability and restlessness in 50% followed by anxiety in 36.36%, reduce sleep in 31.81%, aggressive behavior in 18.18%, In post lockdown highly faced problem is irritability 80%, aggressive behavior 43.3% followed by restlessness 40%, reduce sleep 30%, low mood 16.6% and reduce appetite and craving in 10% with anxiety in 6.6%.

DISCUSSION

Present study was to compare the socio-demographic profile of patient in all three phases. The findings indicated (Table 1) that all participants were male in all three phase and the mean age of the participant in post lockdown is 33.03 + 1.12 followed by 31.06 + 1.05 in pre-lockdown and 29.50 + 7.57 in during lockdown and mean income of the family in prelockdown is 17250 + 11640.3 followed by 15227.3 + 5768.81 in during lockdown and 12316.7 + 6556.67 in post lockdown. Higher participant was married 70% in post lockdown followed by pre-lockdown 50% and during lockdown 45.5%. Higher rate of unmarried participant found in pre-lockdown 46.7% followed by during lockdown 45.5% and 26.7% in post lockdown with the separated no. of participant 9.1% in during lockdown followed by pre and post lockdown is 3.3%. Most of participant were educated till 10th in pre-lockdown 46.7%, post-lockdown 43.3% and during lockdown 31.8% followed by graduate 49.9% in during lockdown, 23.3% in pre-lockdown and 20% in post lockdown and 8th is 20% in post lockdown, 16.6% in pre-lockdown and 9.1% in during lockdown. Regarding employment distinguish in five domain 1st is student which is found 18.2% in lockdown, followed by pre-lockdown 16.7% and 6.7% in post lockdown, 2nd domain is self-employed which is found 36.7% in post lockdown followed by 27.3% in during lockdown and 20% in prelockdown, 3rd domain is employed and most of participant were employed 27.3% in during lockdown followed by 26.7% in post lockdown and 16.7% in pre-lockdown, 4rth domain is part time employed which highly found in during lockdown 13.6% followed by prelockdown 10% and 3.3% in post lockdown, 5th domain is employed most of found in prelockdown 36.7% followed by followed by 26.7% in post-lockdown and 13.6% in during lock-down. And most of participant belongs to joint family 63.3% followed by nuclear family 46.7.

The study was carried out by kelvin et al having the opioid use disorder and alcohol use disorder which were more or less supported to the present study. (Where mean age of the participant were 33.01)

Another aim of the study was to compare the clinical profile of patient in all three phases. The findings emphasized (Table 2) that in pre-lockdown - 50% diagnosed with Alcohol dependence and 50% diagnosed with Opioid Dependence followed by 50-50% in post lockdown and in during lockdown 63.6% of opioid dependence and 36.4% of alcohol dependence. Findings of other substance abuse (including tobacco and cannabinoids) across the sample was 96.7% in pre-lockdown followed by 90% in during lock-down and 73% in post lockdown of participant.

The findings of the present study explored about the physical problems of the people of alcohol and opioid dependence during the covid -19 pandemic (in the all three phases). The findings revealed that 76.7% of the patient felt physical problem (tremors, body aches, stomach cramps). The study indicated that high noise level in the family were found among 60.3% in the patient during lock-down, followed by 60% in pre-lockdown, while 40% in post lockdown. The interpersonal relationship with wife was reported in 13.6% in during lock-down followed by 13.3% in post lockdown, while10% in pre-lockdown. Only 27.3% participant faced legal problem (case for fight, drug trafficking) followed by 23.3% in post lockdown and 10% in pre-lockdown. About Occupational consequences 77.3% reported absenteeism from his job followed by 63.3% in pre-lockdown and 33.3% in post lockdown. With 33% were jobless in pre-lockdown followed by 18.2% in during lock-down and 10% in post lockdown and also reported other type of consequences (debt, stealing, plunder) 53.3% in post-lockdown followed by 27.3% in during lockdown and 6.7% in pre-lockdown and very few member reported that suffering from psychiatric illness 13.3% in post lockdown followed by 9.1% in during lockdown and 6.7% in pre-lockdown and also reported about medical illness 13.3% in pre-lockdown followed by 6.7% in post lockdown and 4.5% in during lockdown with the most of member (36.7%) in post-lockdown reported having family history of substance abuse followed by 36.4% in during lockdown and 16.7% in pre-lockdown. Mean and SD of financial consequences reported by the participant is 1595.5 \pm 1446.9 in during lock-down followed by 1158.5 \pm 1364.2 in post lock-down and 1094.7 <u>+</u> 1470.2 in pre-lockdown.

The aim of this study was to assess psychological problems of the patient with Alcohol use disorder and opioid use disorder in all three phases. The findings emphasize that (Table 2.2) common psychological symptom irritability, aggressive behavior, restlessness, reduce sleep and anxiety in all three phases. Irritability has been found 83.33% in pre-lockdown followed by 80% in post lockdown and 59% in during lockdown phase, regarding aggressive behavior 43.3% found in post lockdown followed by 20% in pre-lockdown and 18.18% in during lockdown, about restlessness 56.6% in pre-lockdown followed by 50% in during lock down and 40% in post lockdown period. Regarding reduce sleep 31.81% in during lockdown followed by 30% in post-lockdown and 6.6% in pre-lockdown, about anxiety 36.36% in during lock down followed by 6.6% in post-lockdown and 3.3% in pre-lockdown phases. Similar study found by Ornell et al, drug use can increase the risks associated with a coronavirus infection, the social and psychological risks of the pandemic can favor and intensify drug abuse, in a potentially catastrophic cycle. Social distance, isolation or quarantine is essential measures to help prevent coronavirus transmission - however, these strategies, and the pandemic outbreak itself, have been associated with negative emotions,

such as irritability, anxiety, fear, sadness, anger. These conditions are known to trigger relapse, even in those long-term abstainers, or intensify drug consumption. Withdrawal symptoms elicited during lockdown could also jeopardize these preventive strategies, as it could drive individuals to go outside for drugs. A study by Chiappini et al also found that COVID-19 and lockdown created many types of psychological problem of people with substance use disorder like anxiety, sleep disorder, reactive behavior and mood & thought disorder.

CONCLUSION

It is easily understandable that COVID-19 spread the threat about been infected and preventing strategy lockdown impacted on humans' life in various area, like physical, mental, social as well as economical problem. People with alcohol and opioid use disorder already faced with many types of problem like social stigma, discrimination, family problem, which leads to avoid taking treatment service. So CVID-19 and lockdown seem a dual pandemic for people with alcohol and opioid use disorder. Problem of lockdown impacted to access treatment services so people with opioid and alcohol dependence were not able to utilize the services resulting service utilization was reduced in lockdown. Need to modification in service delivery system for easy to access in all situations for people with Alcohol and Opioid use disorder.

Limitation

- 1. Small sample size in this study so normal generalization of the result remains doubtful, larger no. of participant could have given better outcome in the field of research.
- 2. Sample not taken equally in all three phases, during lockdown found less sample.

Clinical implication

COVID-19 and lockdown play a critical role for all and especially for people with alcohol & opioid use disorder. Pandemic has been impacted in various areas and all gender and for people with substance use disorder seems a pillar of barrier to access the treatment services. This study will help to address the problems to face by addicts people and problems to success services resulting will help out how to deliver these services in pandemic.

Future direction

- 1. Similar type of study can be conduct on a large sample with prospective deign.
- 2. Further study can be carried out on both sexes to see gender difference.
- 3. Similar study should be repeated on community level.
- 4. Study should be compared with psychiatric comorbidities for better understanding

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Conflict of Interest

The author(s) declared no conflict of interest.

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