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Naltrexone as a Treatment for Heroin Dependence and its Relationship with Depression

Insha Mehraj Kak*, Neelofer Jan and Altaf Ahmad Malla

Department of Psychiatry, Institute of Mental Health and Neuroscience, Kashmir

ABSTRACT

Background: Our study was aimed to know does Naltrexone used in opioid dependent patient have any relation with the onset of depression.

Methods: Naltrexone was given to 30 opioid dependent patients who had undergone inpatient detoxification with no underlying psychiatric comorbidity at baseline. HAM-D was applied at 2,4,6 weeks post Naltrexone initiation.

Results: Our study showed that at 2 weeks, 60% of patients showed depressive symptoms out of which 37% met the criteria for mild depressive disorder and 23% met the criteria for moderate to severe depression. At 4 and 6 weeks, majority continued to be depressive while only 3% of the patients showed improvement in depressive features.

Conclusion: From our study, we concluded that a positive correlation was found between Naltrexone and Depression in Opioid users.

Keywords: Naltrexone; Opioid; Depression

Introduction

There has been a recent heightened concern over heroin use in our community. The rate of fatal overdoses has increased significantly. To overcome this epidemic of heroin use various solutions, including the establishment of supervised injecting facilities, new treatment approaches, and improved prevention programs have been started. Treatment approaches include: drug withdrawal, abstinence based programs, and a variety of pharmacotherapies. Heroin detoxification usually takes 5-7 days and is rarely life threatening. However, the greatest challenge for most patients is to maintain and sustain a drug free lifestyle. Hence, post-withdrawal treatment options are crucial in maintaining behaviour change. Naltrexone is indicated in post-withdrawal relapse prevention intervention. Clinical studies have shown that 50 mg of naltrexone blocks the effects of 25 mg of intravenously administered heroin for more than 24 hours [1]. Naltrexone is a competitive μ receptor antagonist and is used in the treatment of opioid dependence. Naltrexone has a greater affinity for μ receptors than heroin and other opioid agonists. It has a half-life of approximately 2 hours to 6 hours. 6β naltrexol is the major metabolite of naltrexone. Naltrexone has a good side effect profile, does not produce tolerance or dependence. The most common adverse effects were found to be nausea (9.8%), headache (6%), dizziness (4%), nervousness (3%), fatigue (3%), anxiety (2%) and depression (1%). There is conflicting evidence whether depressive symptoms are clinically important adverse effects in patients receiving naltrexone treatment. Some studies have shown that a single dose of naltrexone caused a significant increase in serum cortisol and ACTH levels which is the same as that of depression. Recent estimates indicated a lifetime prevalence of depression among heroin users of 41% and 30% reported a current episode of depression [2].

Aim

This study aims to elucidate any association between depression and Naltrexone treatment in opiate dependent individuals, who have been started on naltrexone maintenance treatment following inpatient detoxification. All patients continued oral naltrexone maintenance for the duration of the 6 weeks.

Materials and Methods

Study settings

The study was conducted from December 2018 to December 2019 in drug and de-addiction centre SMHS Srinagar.

Study design

6 week follow up study.

Study population

A total of 30 patients participated in the study that was started on naltrexone maintenance after undergoing inpatient detoxification. To foster compliance and to reduce the drop outs a close follow up with behavioral Naltrexone therapy which includes motivational enhancement therapy was used.

Inclusion criteria

1. Participants of age more than 18 years.
2. Drug use was detected by using Urine drug screening on a random basis.
3. Patients who completed at least 6 weeks of outpatient maintenance and were adherent to naltrexone.
4. Completed HAM-D at 2, 4, and 6 weeks post baseline.
5. Participants who gave consent for the study.

Corresponding author: Insha Mehraj Kak, Department of Psychiatry, Institute of Mental Health and Neuroscience, Kashmir, Tel: 8716900124; E-mail: drinsha27@gmail.com

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Exclusion criteria

1. Age less than 18 years.
2. Patients who had underlying psychiatric disorders.
3. Patients who did not give consent for the study.

Measures

Semi Structured Performa was used to collect data regarding sociodemographic, M.I.N.I (Mini international neuropsychiatric interview) was administered to cases to diagnose the presence of psychiatric illness in them. Hamilton depression scale was administered at baseline before starting naltrexone then at 2 weeks, 4 weeks, and 6 weeks after maintaining on naltrexone. The primary outcome was assessed by using HAM-D Rating Scale a widely used validated standardized assessment tool used to assess various domains of depression [3]. For the convenience of the study we divided HAM-D into two domain cognitive and somatic. Cognitive domain comprising of depressed mood, guilt, suicidal ideations, insomnia, work and leisure, PMA, Psychic Anxiety and Hypochondriasis and Somatic domain comprising of agitation, somatic anxiety, Gastrointestinal symptoms, general somatic symptoms and weight gain. A urine drug screen was used randomly to confirm opioid free status of the patient throughout the course of the study.

Results

The Table 1 shows that most of the cases were males with a mean age of 28 ± 10 yrs, out of them 53% were unmarried. Most of them were literate (97%) with a formal education till the 8th standard.70% were employed, and 67% belonged to the urban background. Most of them (57%) had good family support. Around 37% of the patients belonged to lower socioeconomic status.

S.NO	SOCIODEMOGRAPHIC VARIABLES	N=30	Ratio
1	Age Mean Age	28 ± 10 YRS	
2	Sex Male; Female	30:0	
3	Marital status Married; Unmarried	14:16	47:53
4	Education Illiterate; literate	4:26	13:87
5	Occupation Working; Not working	21:9	70:30
6	Background Rural; Urban	10:20	33:67
7	Social support Good; Poor	17:13	57:43
8	Socioeconomic status Upper Middle; Lower Middle; Lower	9:10:11	30:33:37

Table 1: Sociodemographic Variables.

The Table 2 shows that 36.7% of patients showed mild depressive symptoms at 2 weeks post naltrexone initiation and at 4 and 6 weeks 33.3% of patients still showed mild depression, 16.6% of patients were found to have moderate depressive features at 2 weeks, at 4 and 6 weeks follow up only 13.3% of patients continued to meet the criteria for moderate depression as per HAM-D. Severe depression was found in 6.7% of the patients with no change in the score at 4 and 6 week follow up. The Table 3 shows that guilt, insomnia, psychic anxiety increased significantly over the study period with the $p<0.01$. The Table 4 shows that among somatic symptom domains of HAMD-D, all the domains increased significantly over time except weight with the $p<0.01$. The Table 5 shows the Pairwise comparison (*Significant at 0.05 level, **Significant at 0.01 level).

Depression	Baseline N=30 F (%)	Second Week N=30 F (%)	Fourth Week N=30 F (%)	Sixth Week N=30 F (%)
No Depression	30 (100)	12 (40)	14 (46.7)	14 (46.7)
Mild Depression	0 (0.00)	11 (36.7)	10 (33.3)	10 (33.3)
Mild to Moderate Depression	0 (0)	5 (16.6)	4 (13.3)	4 (13.3)
Moderate to Severe Depression	0 (0)	2 (6.7)	2 (6.7)	2 (6.7)

Table 2: Severity of depression.

Variables	Baseline Mean ±SD	Second Week Mean ± SD	Fourth Week Mean± SD	Sixth Week Mean± SD	F Value (df=3, 87)	Sig	Partial Eta
DM	1.37 ± .49	1.50 ± .51	1.47 ± .51	1.47 ± .51	2.351	0.78	0.75
Guilt	.833 ± .65	1.23 ± .77	1.23 ± .77	1.27 ± .74	13.17	0.001**	0.312
Suicide	.000 ± .00	.033 ± .183	.033 ± .183	.033 ± .183	1.00	0.397	0.033
Insomnia	1.00 ± .587	1.27 ± .639	1.20 ± .610	1.20 ± .610	5.52	.002**	0.160
Work	.167 ± .38	.233 ± .43	.233 ± .43	.233 ± .43	2.07	0.11	0.067
PMA	.000 ± .00	.033 ± .18	.033 ± .18	.033 ± .18	1.00	0.39	0.033
Anx Psy	.300 ± .59	.768 ± .77	.633 ± .72	.633 ± .72	10.97	.001**	0.274
Hypo	.000 ± .00	.500 ± 1.01	.467 ± 1.01	.467 ± 1.01	6.622	0.061	0.186

Table 3: Cognitive Symptoms of HAM D.

Variables	Baseline (N= 30) Mean ± SD	Second Week (N= 30) Mean ± SD	Fourth Week (N= 30) Mean ± SD	Sixth Week (N= 30) Mean ± SD	F Value (df=3, 87)	Sig	Partial Eta
Agitation	.233 ± .43	.567 ± .68	.467 ± .62	.467 ± .62	5.67	.001**	0.164
Anxiety Som	.133 ± .35	.867 ± .82	.800 ± .81	.800 ± .81	21.91	.001**	0.422
GI	.100 ± .30	.767 ± .43	.767 ± .43	.767 ± .43	58.00	.001**	0.667
General Som	.000 ± .00	.633 ± .49	.633 ± .49	.633 ± .49	50.09	.001**	0.633
Weight	.567 ± .63	.633 ± .61	.600 ± .56	.600 ± .56	0.795	0.500	0.027

Table 4: Somatic Symptoms of HAM D.

Variables	Baseline Vs Second Week Mean Difference (Sig)	Baseline Vs forth Week Mean Difference (Sig)	Baseline Vs sixth Week Mean Difference (Sig)	Second Week Vs Fourth Week Mean Difference (Sig)	Second Week Vs Sixth Week Mean Difference (Sig)	Fourth Week Vs Sixth Week Mean Difference (Sig)
Guilt	-.400 (0.003**)	-.400 (0.003**)	-.433 (0.001**)	0.000 (1.00)	-.033 (1.00)	-.033 (1.00)
Insomnia	-.267 (0.053)	-.200 (0.188)	-.200 (0.188)	0.067 (0.96)	0.067 (0.96)	0.000 (-)
Agitation	-.333 (0.014*)	-.233 (0.194)	-.233 (0.194)	.100 (1.00)	.100 (1.00)	0.000 (-)
Anx_Psy	-.467 (0.001**)	-.333 (0.014*)	-.333 (0.014*)	-133 (0.62)	-133 (0.62)	0.000 (-)
Anx_Som	-.733 (0.001**)	-.667 (0.001**)	-.667 (0.001**)	.067 (0.96)	.067 (0.96)	0.000 (-)
GI_Sx	-.667 (0.001**)	-.667 (0.001**)	-.667 (0.001**)	0.000 (-)	0.000 (-)	0.000 (-)
Gen_Som	-.633 (0.001**)	-.633 (0.001**)	-.633 (0.001**)	0.000 (-)	0.000 (-)	0.000 (-)
Total HAM D	-4.33 (0.001**)	-3.87 (0.001**)	-3.90 (0.001**)	0.47 (1.00)	0.43 (1.00)	-0.03 (1.00)

Table 5: Pairwise comparison (*Significant at 0.05 level, **Significant at 0.01 level).

Discussion

In our study, it was found that opioid dependence is most common among males in the mean age group of 28 years. Our study findings were supported by Mysels et al who found in his study that 91% of opioid dependent were males in the mean age group of 37.2 [4]. In our study it was found that 67% of the cases were from urban population and only 33% came from rural background which could be due to an acceptable pattern of substance use, easy access to resources and reduced social cohesion. This finding was further supported by Catherine et al in her study where she found that substance abuse was most prominent in the urban population [5].

Also 57% of our study participants were found to have good social support which also increased naltrexone adherence in our study.

Around 37% of our cases belonged to lower socioeconomic status. Lower socioeconomic status results in chronic stress which have a negative impact on individuals overall health and mental wellbeing as well as reduced access to resources like education, social support and health services. Also children from lower socioeconomic status background get less supervision and care from their families thereby predisposing them to substance abuse. This study finding was supported by Catherine, et al. which showed that people from lower socioeconomic status have poor health and wellbeing and are more likely to use illicit drugs [5].

In our study, we used the Hamilton Depression rating scale at baseline, 2 weeks, at 4 weeks and 6 weeks after starting Naltrexone. Drug compliance and opioid free status was established by close follow ups, Naltrexone behavioral therapy including motivational interviewing, cognitive behavioural therapy and involvement of close family member and random urine drug sampling. We found that at 2 weeks post naltrexone initiation 18 of 30 patients (60%) had depressive symptoms constituted by 37% of the mild depression and 23% of moderate to severe depression. At 6 weeks post Naltrexone not much significant improvement in HAM-D scores was found, only 3% of the patients improved. At 4 and 6 weeks follow up 53.3% of the cases continued to show depressive features. For the convenience of the study we divided HAM-D into cognitive and somatic domain; Cognitive domain comprising of depressed mood, guilt, suicidal ideations, insomnia, work and leisure, PMA, Psychic Anxiety and Hypochondriasis and Somatic domain comprising of agitation, somatic anxiety, Gastrointestinal symptoms, general somatic symptoms and weight gain. It was found that somatic symptoms predominated than cognitive symptoms. Among somatic domain: gastrointestinal symptoms (loss of appetite, constipation, nausea), general somatic (backache, headache, fatigue, muscle ache), agitation, somatic anxiety was found to increase significantly over 4 and 6 week follow up and among cognitive domain: guilt, psychic anxiety and insomnia were found to have increase. Our study findings showed a positive relation between Naltrexone and depression which could be explained by the endogenous opioid system is involved in mood regulation and Naltrexone being an opioid antagonist results in reduction of neurotransmitters in this system, depressive features can originate from psychological and psychosocial changes associated with drug abuse. Studies have found that Naltrexone causes a rise in luteinizing hormones which is known to be associated with depression and anxiety. A study done by Alison et al where it was stated that the underlying rate of depression is high in opioid abusers and treatment can exacerbate it [6]. Our study was further supported by L.E Hollister, et al. his study reported that Naltrexone caused depression, lack of energy, and gastrointestinal symptoms in his patients. Another study done by Thomas, et al. showed that Naltrexone may induce mild dysphoria though his study sample included former opioid addicts [7].

Conclusion

In our study, a positive correlation was found between opioid abuse and Naltrexone. Opioid addicts who were put on Naltrexone developed depressive symptoms. Most of the patients were found to have depressive symptoms at 2 weeks with not much change in the severity of symptoms over 4 to 6 weeks follow up. These depressive features could be attributed to precipitated withdrawal due to Naltrexone in chronic opioid abusers, other side effects e.g gastrointestinal side effects, somnolence, fatigue, etc that are intrinsic to Naltrexone, Neurobiological changes caused due to Naltrexone and craving in itself can cause distress and dysphoria in opioid abusers. Further studies with more sample size and longer follow up need to be done.

Limitations

The major limitations to our study were:

1. Relatively Small sample size, mostly males and may not be generalized to other populations.
2. Lesser duration of follow up which is not enough to evaluate the neuropsychiatric impacts of Naltrexone.
3. Presence or severity of craving after starting Naltrexone was not quantified by any instrument.

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