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Depression-an Open Label Comparative Study

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Abstract

While Naltrexone is a competitive receptor antagonist, buprenorphine is a partial mu-opioid agonist and kappa antagonist. By removing opioids from the receptors, the partial agonist activity of buprenorphine can induce withdrawal in opioid dependent patients. It is regulated sublingually, sublingual, Though Naltrexone has a more prominent partiality for μ receptors than heroin and other narcotic agonists. Utilizing buprenorphine and naltrexone for treatment aims to reduce illicit opioid use and increase treatment retention. Naltrexone and buprenorphine maintenance treatment has been started in opiate-dependent people, and the goal of our study was to see if there was a link between depression and the medication.

At 2, 4, and 6 weeks, the Naltrexone group's depressive mood was significantly higher than the Buprenorphine group's. The Naltrexone group had significantly more insomnia, psychiatric and somatic anxiety, hypochondriasis, and gastrointestinal symptoms than the Buprenorphine group did. It was discovered that buprenorphine has an antidepressant effect.

We concluded from our research that Buprenorphine was associated with higher HAM-D scores and Naltrexone was associated with depression.

Keywords: Addiction; Addiction Research; Therapy; Addiction Therapy; Naltrexone; Opioid; Buprenorphine

Introduction

In our community, there has been a worrying rise in the use of illegal opioids, and there is growing concern about the rise in heroin use, which can lead to overdoses and other health problems like Hepatitis C infection. Various strategies, such as harm reduction strategies, the establishment of supervised injecting facilities, new treatment strategies, and enhanced prevention programs, have been initiated in an effort to stem the heroin use epidemic. Some treatments include: various maintenance and detoxification techniques. The process of heroin detoxification typically lasts five to seven days and is rarely fatal. However, maintaining a drug-free lifestyle remains the greatest obstacle. As a result, options for post-withdrawal treatment are essential for maintaining behavioral change. Current leading maintenance treatment strategies include antagonistic therapy with naltrexone and opioid replacement therapies with buprenorphine or methadone. While Naltrexone is a competitive receptor antagonist, buprenorphine is a partial mu-opioid agonist and kappa antagonist. By removing opioids from the receptors, the partial agonist activity of buprenorphine can induce withdrawal in opioid dependent patients. Sublingual buprenorphine has a high plasma protein binding capacity and a half-life of 24 to 60 hours. CYP3A4 breaks it down into its active metabolite, nor-buprenorphine. In contrast, Naltrexone, in comparison to heroin and other opioid agonists, has a greater affinity for receptors. 6- Naltrexol is its primary metabolite, and its half-life ranges from two to six hours. Buprenorphine can occasionally cause hepatic toxicity, and its use has also been associated with QT interval prolongation. Its side effects include sedation, constipation, headache, nausea, vomiting, dizziness, and respiratory depression. Additionally, naltrexone does not cause tolerance or dependence and has a favorable side effect profile. The most common side effects were nausea (9%), headache (6%), dizziness (4%), nervousness (3%), fatigue (3%), anxiety (2%), and depression (1%). The therapeutic goal of using buprenorphine and naltrexone is to reduce the use of illegal opioids and increase treatment retention. In post-withdrawal relapse prevention treatment, naltrexone is recommended. A Cochrane meta-analysis by Gowing et al. shows that buprenorphine is superior to clonidine in lowering the overall withdrawal score2. Clinical studies have shown that 50 milligrams of naltrexone blocks the effects of 25 milligrams of intravenously administered heroin for more than 24 hours [1]. For the acceptance stage patient can be begun on 8mg greatest on the very first moment. Buprenorphine ought to be begun 12-24hrs after the last narcotic use, measurements can be changed according to clinical side effects. The clinical opioid withdrawal scale can be used to monitor symptoms for at least two hours following the initial dose. Most extreme suggested portion by the maker for the buprenorphine is 24mgs, dosages up to 32mg has been utilized in certain preliminaries. Buprenorphine's more drawn out half-life and slow separation from narcotic receptors permits once everyday dose. In the context of a harm-reduction strategy, which aims to reduce the use of illicit opioids and the incidence of HIV, hepatitis B, and C, long-term maintenance treatment is frequently required to improve outcomes [2].

There is conflicting evidence whether depressive symptoms are clinically important adverse effects in patients receiving naltrexone and buprenorphine treatment. Recent estimates indicated a lifetime prevalence of depression among heroin users of 41% and 30% reported a current episode of depression [3].

Aim

The aim of this study is to find any association between Naltrexone and buprenorphine treatment and depression in opiate-dependent individuals, who have been started on naltrexone and buprenorphine

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maintenance treatment. All patients continued treatment for the duration of 6-weeks.

Methods

Study settings

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

Study design

6 weeks follow up study

Study population

A total of 61 patients participated in the study, patients were divided into two groups; 30 patients received naltrexone and 31 received buprenorphine for maintenance. Patients were randomly selected for any R_x aid treatments. To foster compliance and to reduce the drop-outs, a close follow up with motivational interviewing was used.

Inclusion criteria

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

Exclusion criteria

- Age less than 18 years.
- Patients who had underlying psychiatric disorders.
- Patients who had underlying medical comorbidity which contraindicated the use of the above medications.

Measures: Semi-Structured Performa was used to collect data regarding socio- demographic, 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 2 weeks, 4 weeks, and 6 weeks after maintaining on naltrexone and buprenorphine. The primary outcome was assessed by using HAM-D Rating Scale a widely used validated standardized assessment tool used to assess various domains of dépression, including mood, cognition, vegetative symptoms, and insomnia [4]. 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 all of the participants were males with a mean age of 28 ±10 yrs, out of them majority were unmarried (53.3-58%). Most of them were literate (77.4-86.7%) with a formal education till the 8th standard. Most were employed (70-80.6%), and most belonged to the urban background (61.2-66.7%). Around 35.4-36.7% of the participants belonged to lower socioeconomic status. The P-value was >0.05, so there wasn't any statistically significant difference in the sociodemography of two groups (Table 1).

Table 1: Sociodemographic profile.

Variable	Frequency (Percentage)		P value
	Buprenorphine group	Naltrexone group	
Mean age± SD	28±10	28±10	
Gender			
Males	31 (100)	30(100)	
Marital status			
Married	13 (41.9%)	**14 (46.7%)**	**>0.05**
Un married	18 (58%)	**16 (53.3%)**	
Residence			
Rural	12 (38.7%)	**10 (33.3%)**	**>0.05**
Urban	19 (61.2%)	**20 (66.7%)**	
Education			
Illiterate	07 (22.5%)	04 (13.3%)	**>0.05**
Literate	24 (77.4%)	26 (86.7%)	
Occupation			
Employed	25 (80.6%)	21 (70%)	**>0.05**
Unemployed	06 (19.3%)	09 (30%)	
Socio economic status			
Upper	10 (32.2%)	09 (30%)	**>0.05**
Middle	10 (32.2%)	10 (33.3%)	
Lower	11 (35.4%)	11 (36.7%)	

Table 2: Cognitive symptoms of HAM-D.

Variable	Buprenorphine Mean ± SD	Naltrexone Mean ± SD	t test score	Df	P-value
DM(2)	1.03 ± 0.54	1.50 ± 0.50	3.45	59	**0.01**
DM(4)	0.87 ± 61	1.46 ± 0.50	4.1		**0**
DM(6)	0.65 ± 0.48	1.46 ± 0.50	6.45		**0**
Guilt (2)	1.09 ± 0.74	1.23 ± 0.77	0.7	59	**0.48**
Guilt (4)	1.16 ± 0.68	1.23 ± 0.77	0.38		**0.7**
Guilt (6)	1.12 ± 0.67	1.26 ± 0.73	0.76		**0.44**
Suicide (2)	0.00 ± 0.00	0.033 ± 0.18	1.01	59	**0.313**
Suicide (4)	0.00 ± 0.00	0.33 ± 0.18	1.01		**0.313**
Suicide (6)	0.00 ± 0.00	0.33 ± 0.18	1.01		**0.313**
Insomnia (2)	1.12 ± 0.42	1.26 ± 0.63	0.99	59	**0.326**
Insomnia (4)	0.80 ± 0.54	1.20 ± 0.61	2.66		**0.01**
Insomnia (6)	0.61 ± 0.49	1.20 ± 0.61	4.13		**0**
Work(2)	0.51 ± 0.56	0.23 ± 0.43	-2.18	59	**0.03**
Work(4)	0.48 ± 0.50	0.23 ± 0.43	-2.07		**0.04**
Work(6)	0.38 ± 0.49	0.23 ± 0.43	-1.29		**0.2**
PMA(2)	0.00 ± 0.00	0.23 ± 0.43	1.01	59	**0.313**
PMA(4)	0.00 ± 0.00	0.33 ± 0.18	1.01		**0.313**
PMA(6)	0.00 ± 0.00	0.33 ± 0.18	1.01		**0.313**
Psy anxiety(2)	0.64 ± 0.66	0.76 ± 0.77	0.66	59	**0.51**
Psy anxiety (4)	0.41 ± 0.56	0.63 ± 0.71	1.29		**0.2**
Psy anxiety (6)	0.16 ± 0.45	0.63 ± 0.71	3.07		**0.003**
Hypochond(2)	0.00 ± 0.00	0.50 ± 1.00	2.76	59	**0.008**
Hypochond(4)		0.46 ± 1.00	2.57		**0.012**
Hypochond (6)		0.46 ± 1.00	2.57		**0.012**

Clinical variables

The table 2 shows that at 2,4 and 6 weeks depressed mood was significant in the Naltrexone group than in Buprenorphine. Insomnia was found to be significantly higher in Naltrexone group at 4 and 6 weeks while not much difference was found at 2 weeks between the two groups. Psychic anxiety was found to be more in Naltrexone group at 2,4 , and 6 weeks with significant difference at 6 weeks. Hypochondriasis also was found significantly higher in Naltrexone group than in Buprenorphine group (Table 2).

Psychomotor agitation was found to be more in Naltrexone group at 2,4, and 6 weeks with significant difference at 6weeks. Somatic anxiety, gastrointestinal symptoms and genital symptoms were significantly more in Naltrexone group throughout study period than Buprenorphine group (Table 3).

Table 3: Somatic symptoms of HAM-D.

Variable	Buprenorphine Mean ± SD	Naltrexone Mean ± -SD	t Test score	df	P-value
Agitation (2)	0.45 ± 0.50	0.56 ± 0.67	0.75	59	**0.45**
Agitation (4)	0.29 ± 0.46	0.466 ± 0.62	1.25		**0.21**
Agitation (6)	0.16 ± 0.37	0.466 ± 0.62	2.31		**0.02**
Anx som(2)	0.12 ± 0.34	0.86 ± 0.81	4.61	59	**0**
Anx som(4)	0.09 ± 0.33	0.88 ± 0.80	4.54		**0**
Anx som(6)	0.03 ± 0.17	0.88 ± 0.80	5.17		**0**
GI (2)	0.96 ± 0.30	0.76 ± 0.43	7.07	59	**0**
GI (4)	0.03 ± 0.17	0.76 ± 0.43	8.75		**0**
GI (6)	0.00 ± 0.00	0.76 ± 0.43	9.92		**0**
Gen som (2)	0.00 ± 0.00	0.63 ± 0.49	7.19	59	**0**
Gen som (4)	0.00 ± 0.00	0.63 ± 0.49	7.19		**0**
Gen som (6)	0.00 ± 0.00	0.63 ± 0.49	7.17		**0**
Weight (2)	0.67 ± 0.59	0.63 ± 0.61	-0.02	59	**0.77**
Weight (4)	0.67 ± 0.59	0.60 ± 0.56	-0.52		**0.6**
Weight (6)	0.67 ± 0.59	0.60 ± 0.56	-0.52		**0.6**

Discussion

Opioid receptors are recently been implicated to play role in the regulation of mood and emotional behavior's. Kappa receptors (K-receptor) particularly have a role in mood regulation. Dynorphins are endogenous neuropeptides that activate K- receptor. Both K- receptors and these endogenous ligands are highly expressed in brain regions that mediate stress response, cognitive and reward behaviors. Activation of K-receptors by endogenous ligands or their agonist's leads to pro-depressive like behavior. In contrast K- receptor blockade with high affinity κ-receptor antagonists, such as norbinaltorphimine (norBNI), effectively reduce stress induced pro-depressive-like behaviours and have antidepressant-like and anxiolytic-like effects in rodents. Buprenorphine is a semi-synthetic opioid with a unique complex pharmacology. Buprenorphine acts as a partial μ-receptor agonist and a κ-receptor antagonist with additional nociception/orphanin FQ receptor (NOP-receptor, also known as ORL1) partial agonist activity. Clinically, buprenorphine is used as a potent analgesic and as an alternative to methadone in the treatment of opioid addiction. In addition, buprenorphine has been shown to be effective in a small cohort of treatment-resistant depressed patients, with clinical improvement evident within one week of treatment. Recently, buprenorphine has also been shown to have antidepressant- and anxiolytic-like activity in mice.

Sociodemographic profile

In our study, it was found that opioid dependence is most common among males in the mean age group of 28 years, which is expected as male gender is the accepted risk factor for substance use disorders including opioids. Our study findings are in line with study by Mysels et al who found that 91% of opioid-dependent were males in the mean age group of 37.2 [5]. We found our study that 61.2-66.7% of the cases were from urban population which may be due to myriad of factors including easy access to substances, an acceptable pattern of substance use, 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 [6].

Around 35.4-36.7% of the participants belonged to lower socioeconomic status. This could be because lower socioeconomic status puts individuals under the risk of chronic stress due to many reasons like lack of resources to support basic physiologic needs, lack of education, social support and health services which in-turn has a negative impact on individuals overall health and mental well-being. Also children from lower socioeconomic status background get less supervision and care from their families thereby predisposing them to substance abuse. These study findings was supported by Catherine et al which showed that people from lower socioeconomic status have poor health and well-being and are more likely to use illicit drugs [6].

In our study, we used the Hamilton Depression rating scale at baseline, 2 weeks, at 4 weeks and 6 weeks after starting Naltrexone or buprenorphine. Drug compliance and opioid free status was established by close follow ups, Naltrexone behavioral therapy including motivational interviewing, cognitive behavioral 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: Psychomotor agitation was found to be more in Naltrexone group at 2,4, and 6 weeks with significant difference at 6weeks. Somatic anxiety, gastrointestinal symptoms and genital symptoms were significantly more in Naltrexone group throughout study period than Buprenorphine group and among cognitive domain: depressed mood was significantly more in the Naltrexone group than in Buprenorphine throughout study period. While there was't much difference in the ratings of insomnia between the two groups during initial two weeks Insomnia was found to be significantly higher in Naltrexone group at 4 and 6 weeks which could be explained because of initial severe withdrawals hampering sleep in both groups equally. Also Psychic anxiety was found to be more in Naltrexone group at 2,4 , and 6 weeks with significant difference at 6 weeks and hypochondriasis was also significantly higher in Naltrexone group than in Buprenorphine group. Although, the ratings on problems with work and leisure apparently are more in buprenorphine group but this domain of HAM-D was initially affected more in buprenorphine group and it improved over time in this group though there was no such change in this domain in the naltrexone group over time.

Our study findings showed that while there was a linear relation between Naltrexone and increased scores at HAM-D which is mainly contributed by high scores in various somatic domains, there was no such relation found with the use of buprenorphine, in-fact there was improvement in most of the domains of HAM-D in the buprenorphine group. These changes could be explained on the basis of involvement of endogenous opioid system in mood regulation and Naltrexone being an opioid antagonist results in reduction of neurotransmitters in this system, while buprenorphine being an K- antagonist alleviates the depressive features. Studies have also found that Naltrexone causes a rise in luteinising hormones which is known to be associated with

depression and anxiety while buprenorphine blocks stress induced pro-depressive effects of various endogenous endorphins resulting in alleviation of depression and anxiety. 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 [7]. Another study done by Thomas et al. showed that Naltrexone may induce mild dysphoria though his study sample included former opioid addicts [8]. Also study by A. Almatroudi et al. has shown that combined administration of buprenorphine and naltrexone produces antidepressant- like effects in mice [9].

Conflict of Interest

None

Acknowledgement

None

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