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Low-dose and high-dose naltrexone in opioid dependence syndrome: a three months outcome study

Abstract

Background: Naltrexone is effective in the treatment of opioid dependence syndrome (ODS) as it prevents relapse. To effectively design a cost-effective treatment modality for ODS using naltrexone as low as 25 mg is something which is worth exploring. **Aim:** To study the effectiveness of 25 mg naltrexone and 50 mg naltrexone in patients with ODS. **Materials and methods:** Case record files of patients of ODS admitted in psychiatry ward from January 2015 to September 2017 were retrieved and analysed after applying coding plan. **Results:** A total of 79 patients with ODS were admitted during this period. Patients were divided into three groups- group one received 25 mg naltrexone per day, group two: 50 mg naltrexone, and group three: non-naltrexone. Cumulative abstinence duration (CAD) in group one was 48 days, group two was 52 days, and group three was 23 days. At follow-up, there was no relationship between abstinence status and dose of naltrexone prescribed and amount of opioid use. **Conclusion**: Naltrexone is effective in reduction of craving and there was no significant difference between the different dosages of naltrexone, i.e. 25 mg and 50 mg per day.

Keywords: Psychiatry. Craving. Dosage.

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INTRODUCTION

Opioid dependence is a serious public health issue. Naltrexone is a pure opioid antagonist which completely blocks the subjective and other effects of opioid, when administered to detoxified opioid dependent patients. Naltrexone prevents relapse and helps to maintain abstinence.[1] The major problem with naltrexone is poor compliance and high relapse rate, particularly in countries in which there is a treatment alternative based on substitution of illicit opioid with orally administered partial agonist/antagonists (buprenorphine). According to a study, 91% of the inpatients relapsed during follow-up after discharge and out which 59% cases relapsed within the first one week.[2]

Naltrexone in a 50 mg dose was approved by the US Food and Drug Administration (FDA) as a treatment for heroin addiction way back in 1984. As per a Norwegian study, low-dose naltrexone (LDN), i.e. 5 mg per day use has led to reduction in opioid use in patients who used LDN more than once. The study showed a dose-response relationship between increasing LDN exposure and reduction in total opioid use and increasing time to first opioid prescription after starting LDN. Initiation of LDN was followed by a 46% reduction in opioid prescriptions per annum. The reduction of opioid use was not compensated by increased use of other prescribed painkillers.[3] Surprisingly, around two to three million prescription opioid abusers are not receiving any sort of treatment,[4] and those who enter often only seek detoxification, which ultimately land up in early relapse and which is the most common outcome in opioid dependent patients. The most successful treatment in opioid dependence is long-term maintenance therapy.[5]

Experimental studies with chronic administration of opioid (morphine) to pre- and postnatal rats showed a marked decrease in μ-opioid receptor density in brain without a change in receptor affinity with no remarkable changes seen in other opioid receptors, namely δ- or κ-receptors. This down-regulation was accompanied by tolerance to the analgesic effects of the opioid. And importantly, long-term treatment produced no further change in opioid receptors. Demonstration of in vivo down-regulation of brain μ-opioid receptors following opioid (morphine) administration provides evidence for a unique plasticity of the immature opioid receptor system.[6]

Opioid abstinence leads to up-regulation of μ-opioid receptors, mainly in the hypothalamic region of the brain.[7] Oral naltrexone is available in market for almost two decades; but, there is handful of research[7] on naltrexone 50 mg per day in opioid dependence syndrome (ODS) from India and none on naltrexone 25 mg per day. Oral naltrexone 50 mg per day is an effective dose for prevention of relapse; but, we do not have data whether 25 mg naltrexone will also be effective or not or no better than placebo.

Although naltrexone 25 mg is available in India and was marketed to counter and the side effect of high-dose naltrexone (HDN), mainly nausea, there are hardly much studies which has reported the effectiveness of the 25 mg dosage preparation in opioid deaddiction. Hence, the current study was planned to compare the efficacy of 25 mg and 50 mg oral naltrexone for relapse prevention in patients with ODS.

MATERIALS AND METHODS

Patients with ODS (as per ICD-10),[8] who were admitted in the deaddiction ward of the Department of Psychiatry, Government Medical College and Hospital, Chandigarh, India from 1st January 2015 to 30th September 2017 were inducted in the study. As a treatment protocol in the department, all the patients of ODS are worked up in detail, severity of withdrawals are assessed by using standard tools like the clinical opiate withdrawal scale (COWS)[9] at admission and discharge. Generally, either of the two different dosages of naltrexone is prescribed to the patients, i.e. 25 mg and 50 mg naltrexone per day. Dose of naltrexone predominately depends upon various clinical parameters and affordability of individual. All the patients receive non-pharmacological treatment in the form of motivation enhancement therapy and relapse prevention therapy. The average duration of inpatients treatment is two weeks and outpatient department (OPD) follow-up visits are done every two weeks. It is also a standard procedure to obtain written consent for treatment from the patients at the time of admission in deaddiction ward of the department.

Case record files of all the admitted patients with ODS during aforementioned time period were taken out and assessed and analysed for sociodemographic, clinical, cumulative abstinence duration (CAD), and type of treatment after applying the coding system. As a standard follow-up progress notes of the patients after discharge from hospital, the craving is recorded as "+" (mild/no craving), "++" (moderate craving), and "+++" (significant severe craving) by the concerned consultant in-charge. On a visual analogue scale in the range of zero to ten points score, "+" meant a score of zero to three signifying no or mild craving, "++" meant a score of four to six signifying moderate craving, and any score above six was designated as "+++" signifying severe craving. Average of all the group members was calculated and accordingly the group was scored. For the purpose of study, abstinence is taken as no use of opioid after the discharge from the deaddiction ward to till three months. Occasional use/intermittent use meant use of opioid one to two times during last two weeks without any socio-occupational dysfunction, and relapse means regular use of opioid during the past two weeks. CAD was calculated on the basis of number of days the patients remained abstinent from illicit opioid use during follow-up period of three months. Patients who were dropped out of follow-up before three months, the same parameters were assessed telephonically.

The patients were divided into three groups, depending upon the dose of naltrexone and other treatment- group one: LDN (25 mg/d), group two: HDN (50 mg/d), and group three: other pharmacological (benzodiazepines, non-steroidal anti-inflammatory drugs [NSAID]/no anti-craving treatment). Here, it is pertinent to mention that as a protocol in the department, the different treatment modalities are discussed with the patients and family members, and based on their withdrawal status, willingness, and affordability for naltrexone, the treatment is started. As the group three participants did not receive naltrexone, so this group also served as the control group in the current study.

As this was a retrospective study, where the patients received treatment as a part of the service provided by the hospital, hence ethical clearance was not sought. However, we would like to mention that it is a prerequisite for admission in deaddiction ward to take written consent for hospitalisation and treatment from the patient.

Statistical analysis

All analyses were conducted using SPSS for Windows (version 16.0; SPSS Inc., Chicago, IL, USA). Discrete categorical data are presented as n (%); continuous data are given as mean. Normality of quantitative data was checked by measures of Kolmogorov-Smirnov tests of normality. For skewed data, Kruskal-Wallis test was used. For normally distributed data, one way ANOVA was applied. For categorical data, comparisons were made by Pearson Chi-square test. All statistical tests were performed at a significance level of $\alpha=0.05$.

RESULTS

A total of 79 patients with ODS were inducted in the study. Out of 79 patients, 14 patients were in 25 mg naltrexone group (group one), 20 patients were in 50 mg naltrexone group (group two), and 45 patients were in the control group (group three) who were prescribed other treatment. All the patients were detoxified with clonidine, and pain killers (NSAID), and benzodiazepines.

Patients in all the three groups were comparable on sociodemographic and clinical parameters, i.e. type of opioid, duration of use/dependence, route of administration, and past history of treatment (Table 1). However, there was small number of female patients in HDN and non-naltrexone groups; but, difference was not significant.

Table 2 shows that CAD in LDN and HDN was comparatively higher than non-naltrexone group; however, it was statistically not significant. Similarly, there was significant reduction in COWS scores from baseline to at the time of discharge in both the naltrexone groups whereas the score in non-naltrexone still fell in the mild category at the time of discharge and the difference was statistically significant ($p=0.000$).

DISCUSSION

Naltrexone leads to significant reduction in craving and helps in maintaining abstinence. CAD in LDN and HDN is close to 50 days out of total 90 days of follow-up period. Hence, both LDN and HDN are equally effective, which is similar to other study with LDN use in neurological, mood disorders, and immuno-comprised patients.[10]

Naltrexone is effective in reduction of craving and maintaining abstinence in individuals with ODS when compared with other non-naltrexone treatment (except

Table 1: Comparison of sociodemographic characteristics amongst the three groups of patients

Variable	Category	Group 1: 25 mg naltrexone (LDN) (n=14)	Group 2: 50 mg naltrexone (HDN) (n=20)	Group 3: No naltrexone (n=45)
Age (in years)	Mean	26.64±6.7	28.25±8.83	31.93±10.87
Gender	Male	100%	95%	91%
	Female	0	5%	9%
Background	Rural	50%	60%	70%
	Urban	50%	40%	30%
Married	Yes	48%	55%	60%
	No	52%	45%	40%
Occupation	Unemployed	14%	35%	26%
	Farmer	21%	10%	13%
	Pvt. job	21%	35%	31%
	Govt. job	7%	0	1%
	Student	37%	20%	24%
Formal education years	Under-Graduate	68%	60%	55%
	Graduate and above	32%	40%	45%

LDN=Low-Dose Naltrexone, HDN=High-Dose Naltrexone

Table 2: Substance use and 3-month follow-up, cumulative abstinence days (CAD)

Variable	Group 1: LDN	Group 2: HDN	Group 3: Non-naltrexone	t (df)	p-value
CAD in days	48.71±69.43	52.35±68.54	23.55±39.60	2.138 (2)	0.089^{NS}
Craving	+	++	+		
Compliance	18%	17%	10%		
COWS					
At Admission	11.64±6.60	15.6±8.44	7.11±7.10	4.194 (2)	0.000*
At discharge	1	1	8	0.020 (2)	0.944^{NS}
Medicine	25 mg naltrexone	50 mg naltrexone	Clonidine, Flupirtine, Ketorolac, BDZs		

LDN=Low-Dose Naltrexone, HDN=High-Dose Naltrexone, COWS=Clinical Opiate Withdrawal Scale, BDZs=benzodiazepines, t=t-test, df=degree of freedom, p^{NS}=not significant, *=p significant

substitution therapy) and same has been reported in earlier studies also.[11]

Convenience of dose is one of the reasons for better compliance. Since, naltrexone is given once in a day which is likely to increase the compliance to treatment and hence, abstinence and same has been reported in earlier research.[12]

Affordability is one of the reasons for non-compliance to treatment.[13] Both dosages of naltrexone have almost equal effect; hence, 25 mg naltrexone cut down the per day cost to half and which can increase the possibility of adherence to treatment.

Although we did not report any significant side effect with either of the dosages of naltrexone, but HDN (50 mg) per day is associated with side effects[14] and 25 mg per day will further reduce the probability of side effects and increase the compliance.

The findings of the current study raise the question that if 25 mg naltrexone per day in patients with ODS is as effective as 50 mg per day, then why to use naltrexone 50 mg per day?

The study was an "intent to treat" analysis which had some limitations. It had a small sample size and shorter duration of follow-up. Also, the fact that LDN was prescribed to patients who had low COWS score and the control group was very heterogeneous in terms of the medications used; so, the fact that its CAD were less than either of the naltrexone group should be interpreted with caution. Nevertheless, the study does point out that LDN (25mg/day) of naltrexone is a good treatment option in ODS and probably this is the first study from India to highlight this fact.

Conclusion

The findings of the current study suggest that naltrexone is a good option to retain patients of ODS. Both doses of naltrexone, i.e. 25 mg and 50 mg per day significantly reduce the craving and are effective in maintaining the abstinence; LDN is likely to be effective in those who have less severe withdrawal during admission for detoxification. As there is no significant difference between the two dosages of naltrexone, hence LDN (25 mg/day) definitely reduces the cost of treatment to half which further increases the chances

of retention in treatment for a longer period. The current study opens new vista to carry out prospective study with two dosages of naltrexone, i.e. 25 mg and 50 mg per day with baseline assessment of severity of ODS and motivation with longer follow-up to strengthen the findings of current study.

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