Original article

Short Term Efficacy Of Buprenorphine–Naloxone+Moxonidine Versus Buprenorphine–Naloxone+Clonidine For Detoxification In Opioid Dependence Followed By Three Months Efficacy Of Naltrexone In Relapse Prevention

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Abstract

Background*: Opioid dependence is a global public health problem with multiple challenging aspects. Various treatment interventions for Opioid Use Disorders (OUD) include detoxification, abstinence- oriented treatments with either Buprenorphine or Methadone and some newer drugs including Clonidine and Moxonidine. Clonidine enantiomer, Moxonidine has shown efficacy in opioid withdrawal state. However, no study has compared it with Clonidine directly, hence, present study compared short- term efficacy of Moxonidine versus Clonidine for opioid detoxification followed by three-month efficacy of Naltrexone for relapse prevention.*

Method*: 126 patients of OUD as per DSM-5 criteria were enrolled in a hospital based open-label study. After recording socio-demographic data and screening on Drug Abuse Screening Test (DAST), patients were randomly assigned into (63 each): Group-A –Buprenorphine-Naloxone (BPX) + Moxonidine and Group-B - Buprenorphine-Naloxone (BPX) + Clonidine. Primary outcome measures were clinical improvement on Clinical Global Impression (CGI-S) scale, Clinical Opioid Withdrawal Scale (COWS), Subjective Opioid Withdrawal Scale (SOWS) and Visual Analogue Scale (VAS) at baseline, seven and 14 days. Secondary outcomes measures were quality of life and adverse drug reactions. Patients were then followed up for 3 months on Naltrexone.*

Results*: Though CGI-S score significantly reduced from baseline to 7 days and 14 days in Group B (5.57±0.50; 4.21±0.41 and 1.25±0.44, respectively) and Group A (5.52±0.50; 4.22±0.42 and 2.38±0.49, respectively), but significantly more in group B (p<0.001). Mean COWS score reduced significantly more from baseline to 14 days in Group B (27.79±5.01 to 8.49±2.16) than Group A (27.89±4.97 to 9.22±1.94) with p=0.048. Similarly, significantly more reduction in SOWS score (p=0.042) and VAS score (p<0.001) in Group B as compared to Group A.*

Conclusion*: Clonidine is more efficacious than Moxonidine in combination with BPX for short-term detoxification in OUD.*

Key-words*: Clonidine, Moxonidine, Apha-2 adrenergic receptors, Imidazoline receptors.*

Introduction

Currently, opioid detoxification protocols in vogue are either BPX (buprenorphine plus naloxone), Methadone or Tramadol/ Tapentadol or in combinatorial regimen.[1,2] Various treatment guidelines suggest that Buprenorphine (partial opioid agonist at mu receptors and a weak antagonist at kappa receptors) is effective for opioid detoxification.[3,4] Clonidine has been used in one of the regimens to reduce autonomic symptoms.[5] A role for imidazoline receptors in reward pathways [6] has been postulated and Moxonidine (imidazoline 1 agonist) found beneficial in withdrawal.[7]

Prevention of relapse is often challenging which occur in majority cases within a year, mostly first three months.[9] Naltrexone (opioid receptor antagonist) is the approved treatment of choice for relapse prevention.[8]

Since moxonidine and clonidine have different receptor profile, so present study was planned to compare the efficacy of Moxonidine in comparison to Clonidine in combination with BPX for short-term detoxification (based upon clinical and symptomatic improvement). Sustainability on antagonist (Naltrexone) was compared during follow-up of 3 months and assessed on survival analysis (drop out).

Materials and Methods

It was a hospital-based, open-label, interventional, comparative, and follow-up study, done on patients admitted at a 50 bedded Model Deaddiction Centre of Department of Psychiatry of a tertiary care medical college & hospital in north India. Data was collected from December 2021 till December 2022.

Sample size calculation: error (d) = Two Tailed 0.05, Power (1–α) = 0.8, Standard Deviation = 1.00 , Zα = 1.95996. Zβ = 0.84162)

$$N = \frac{2 \times \{S.D \times (Z\,\alpha/2 + Z\,\beta)\}^2}{D^2}$$

N = 126 (A = 63, B = 63)

Inclusion Criteria

1. Age group of 18 to 50 yrs.
2. The patient fulfilled the criteria of opioid use disorder as per DSM-5.
3. Patients were in a withdrawal state at the time of admission (fulfilling the DSM-5 criteria of opioid withdrawal syndrome).
4. Patients who gave voluntary informed consent for detoxification.

Exclusion Criteria

1. Patients diagnosed with any major physical illness, organic brain disease, epilepsy, schizophrenia, other psychosis, mood disorders or mental retardation. These disorders were ruled out clinically by 2 qualified psychiatrists.
2. Patients suffering from any other substance use disorders (ruled out with clinical history as obtained from patients and caregivers) except nicotine.
3. Patients whose BP was ≤90/60 mmHg at presentation were excluded for the risk of severe hypotension.
4. Patients with bradycardia (heart rate <50 beats/minute), severe brady arrhythmia, malignant arrhythmia, heart failure, or severe renal impairment.
5. Pregnant and breastfeeding women.
6. Patients on Beta blockers, Calcium channel blockers, Tricyclic antidepressants, and Digitalis that interact adversely with Clonidine

Tools and Instruments

1. Performa for Socio-demographic variables: Patients will be assessed for substance related clinical variables (duration and dose of opioid use, health hazards related to opioid consumption, past treatment attempts, and quantity of substance used and whether it was natural, semisynthetic or synthetic) and sociodemographic data (age, socioeconomic status, marital status, level of education, occupation, and residence) on semi-structural performa.
2. Drug Abuse Screening Test (DAST-10 item scale): It was given by Harvard and Skinner in 1982 and was designed to provide a brief, self-report instrument for population screening, clinical case finding, and treatment evaluation research. High scores on DAST tend to engage in reckless and impulsive actions. A score of six or more is indicative of the requirement for intensive action.[10]
3. Clinical Global Impression (CGI): It is a 3-item observer scale that is used to measure illness severity (CGI-S) and improvement or change from the initiation of treatment (CGI-I) and therapeutic response. The CGI is rated on a 7-

point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (most severely ill patients). CGI-I scores range from 1 (very much improved) to 7 (very much worse). Each component of the CGI is rated separately; the instrument does not yield a global score.[11]

4. Clinical Opiate Withdrawal Scale (COWS): It was published by Wesson and Ling (2003). The scale consists of 11 points to assess withdrawal symptoms which include- resting pulse rate, sweating, restlessness, pupil size, bone or joint aches, running nose, GI upset, tremors, yawning, anxiety or irritability, and gooseflesh skin. Out of total score of 48 severity is calculated as a score of 5- 12 = mild withdrawal; 13-24 = moderate withdrawal; 25-36 = moderately severe withdrawal; more than 36 = severe withdrawal.[12]
5. Subjective Opiate Withdrawal Scale (SOWS): Subjective symptoms and discomfort experienced by the patient and their intensity are recorded on this scale under 16 points which were filled by the patient. Scale for every point ranges from 0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, and 4= extremely. The severity of symptoms was assessed as mild withdrawal with a score of 1 – 10, moderate withdrawal with a score of 11 – 20, and severe withdrawal with a score of 21 – 30.[13]
6. Visual Analogue Scale (VAS): It was given by McMillan and Gilmore-Thomas in 1996. It is the most frequently used procedure to measure craving in the previous 24 hours where the subject quantifies his/her subjective state of craving by marking a point on the line which is anchored at one end by words as 'no craving at all' and at the other end as 'strongest craving ever'.[14]
7. SF-36 Short-Form Health Survey (SF-36): The SF-36 consists of eight scaled scores, each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The higher the score the less disability that is a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability. The eight sections include vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health.[15]
8. Adverse drug reaction performa was used to assess adverse drug reactions arising during the treatment: It was given for voluntary reporting of ADR by healthcare professionals. A reaction is regarded as serious when the patient outcome is death, life-threatening, hospitalization, disability, congenital anomaly or requires intervention to prevent permanent damage.[16]

Outcome Measures: Primary outcome measures include the success of detoxification on a negative urine screening, therapeutic efficacy on CGI, improvement in withdrawal symptoms on the COWS and SOWS and craving assessment on VAS. Secondary outcome measures include well-being on SF–36 scale, retention on Naltrexone and relapse rate in three-month follow-up.

***Study protocol*:** 126 patients diagnosed with OUD (as per DSM-5 criteria) who gave written informed consent and fulfilled the inclusion criteria were further screened on Drug Abuse Screening Test (DAST). Severity was assessed as per DSM-5 criteria into mild, moderate and severe. Baseline vitals were recorded at the time of examination and routine blood investigations including viral markers were done. The methadone equivalents were then converted to Buprenorphine (BPN) to control for the bias that may be linked to various formulations of opioid/raw or synthetic drugs consumed in. The socio-demographic variables like age, gender, occupation, locality, and marital status were recorded. Opiates and synthetic opioids were converted to BPN equivalents as per the operational guidelines for the management of opioid dependence in the South-East Asian region by WHO i.e., Methadone 10 mg=Morphine 40 mg=Buprenorphine 0.4 mg. Patients were randomly divided into 2 groups (63 patients each): Group A received Moxonidine along with BPX and Group B received Clonidine along with BPX.

A flexible dosing regimen [3][4] was used with starting dose of BPX 2-4 mg stat when patient was in moderate withdrawal state (COWS score > 12) and then repeating as per withdrawal symptoms every 2-4 hrs with a total dose of 6-8 mg on Day 1 and increased up to 12 mg/day in some cases. Clonidine and Moxonidine were started when tapering the BPN doses on Day 3 onwards (tapered by reducing 1 mg every alternate day and even faster in some patients depending on their withdrawal symptoms). Dose of 0.1-0.2 mg two to three times a day with a total dose of up to 0.4-0.6 mg/day was started. Assessments were done on COWS and SOWS for withdrawal symptoms, VAS for

craving, and CGI for clinical improvement at baseline, 7 days, and 14 days. Quality of life on SF-36 was assessed at baseline and then at 14 days. BPX, clonidine and moxonidine were stopped on day 14 in all the patients since they were withdrawal free (except for craving in some patients) and further Naltrexone was planned for relapse prevention.
NCT was done 1 week after stopping BPX. 42 patients in Group A and 50 patients in Group B successfully completed NCT and were then prescribed Naltrexone 50 mg to be followed up every month in OPD for the next 3 months for retention on Naltrexone or relapse (who stopped taking Naltrexone or who did not maintain abstinence from opioid use).

***Ethical Considerations*:** The CONSORT Guidelines for clinical trials were adhered to. Treatment was given as per the Good Clinical Psychiatric Practice guidelines of the American Psychiatric Association (APA) guidelines and IPS guidelines. The study was approved by the Faculty of Medical Sciences, BFUHS, Faridkot Punjab vide reference no. 14861 dated 15-12-2021 to conduct the research as per the declaration of Helsinki, Geneva.
CTRI registration: The study was conducted after CTRI approval vide number: REF/2021/12/050198 H.

***Statistical Analysis*:** The observations were statistically analyzed using the software SPSS 24. Demographic variables were compared among the groups using Fisher's exact value. Descriptive data are presented as frequencies with percentage and Mean ±SD for categorical and continuous variables, respectively. Demographic variables were compared among the groups using Fisher's exact value. Comparison of categorical variables was done using Pearson's Chi Square test. Changes in mean scores in the same group at different intervals and differences between the groups were analyzed using paired t-test. P-value < 0.05 and confidence interval of 95% was considered statistically significant. ADRs were calculated and compared between the groups using Fisher's exact test.

Observations & Results
During the study period, total 157 patients with OUD came to Psychiatry OPD of the institute. Out of these, 31 were excluded because of various reasons (16 patients wanted OPD treatment, 4 patients did not give consent for the study, 6 patients were aged >50 yrs and 5 were <18 yrs). The data collection was stopped after inclusion of 126 patients. The mean age of patients in Group A (Moxonidine) was 30.35 ± 8.11 years and in Group B (Clonidine) was 28.87 ± 5.91 years as shown in table 1. The two groups were not statistically different on any of the sociodemographic and clinical parameters.
Majority of the patients used heroin, smack, or brown sugar (88.9% in Group A and 85.7% in Group B) with the intravenous route of administration (>75% in both groups). The mean score on Drug Abuse Screening Test (DAST) was 7.84 ± 1.12 in 67 Group A and 8.11 ± 1.54 in Group B (a score of >6 indicates the need for intensive action). Majority of the patients had severe dependence as per DSM- 5 OUD criteria (66.7% in Group A and 63.5% in Group B).
Table 2 show changes in mean scores in both the groups on the scales. It was seen that CGI-S score improved significantly from baseline (severely ill) to day 7 (moderately ill) and day 14 (borderline ill in group A and normal in group B) in both the groups. Further, the improvement seen in the clonidine group was statistically significantly higher than the moxonidine group (borderline ill in moxonidine group and normal in clonidine group; p value<0.001**). Similarly, the mean CGI-I indicated clinical improvement from "minimally improved" at 7 days to "very much improved" in both the groups, whereas the difference in improvement was significantly more in Group B as compared to Group A (p<0.001**).
Total mean score of COWS shown in table 2 improved from 'moderately severe' withdrawal at baseline to 'mild' withdrawal after 14 days in both the groups. However, the improvement seen in clonidine group was statistically higher at 14 days as compared to moxonidine group (p=0.048*). On comparison of mean scores of individual items in COWS scale in table 3, all the items showed significant improvement from baseline to 14 days in both the groups. However, statistically significant improvement was seen in clonidine group as compared to moxonidine group in

symptoms like resting pulse rate; p=0.005*, sweating; p=0.021*, body or joint aches; p=0.001*, GI upset; p<0.001**, yawning; p<0.001**, anxiety or irritability; p<0.001** and gooseflesh skin; p=0.001**.
Total mean score of SOWS shown in table 2 improved from 'severe' withdrawal at baseline to 'mild' withdrawal at the end of 14 days in both the groups. However, the improvement seen in clonidine group was statistically higher at 14 days as compared to moxonidine group (p=0.042*).On comparison of the mean score of individual items on SOWS scale in table 4, all the symptoms showed significant improvement from baseline to 14 days in both the groups. However, statistically significant improvement was seen in Group B as compared to Group A in symptoms namely perspiration (p=0.008*), running nose (p=0.026*), goose bumps (p<0.001**), shaking (p=0.001*), hot flushes (p=0.002*), cold flushes (p=0.010*), muscle aches (p=0.018*), nausea (p<0.001**), vomiting (p<0.001**), muscle twitching (p=0.001*) and feeling like using now (p<0.001**).
None of the symptoms on both the scales (COWS and SOWS showed significantly higher improvement with moxinidine as compared to clonidine).
Both the drugs significantly reduced craving from baseline to day 7 and day 14 as seen from mean score of VAS (table 2). However, craving reduced statistically more clonidine group as compared to moxonidine group at both day 7 (p<0.001**) and day 14 (p<0.001**).
Means score of SF-36 showed improvement in quality of life in all the domains from baseline to 14 days in both the groups. However, the improvement seen in clonidine group was statistically significantly higher as compared to moxonidine group among domains of physical functioning (p<0.001**), role limitation due to physical health (p<0.001**), energy/fatigue (p<0.001**), emotional well-being (p<0.001**), social functioning (p<0.001**) and general health (p<0.001**).

Naloxone Challenge Test was successfully completed (hence naltrexone was prescribed) by 42 patients out of 63 (66.7%) in moxonidine group and 50 patients out of 63 (79.4%) in clonidine group as shown in table 5 (mild withdrawal was seen in the rest of the patients and they were not prescribed naltrexone). Out of 42 patients in moxonidine group, 34 (80.9%) continued taking Naltrexone at the end of one month followed by 28 (82.3%) at the end of two months and 24 (85.7%) patients at the end of three months. In clonidine group out of 50 patients, 39 (78%) continued taking Naltrexone at the end of one month, 31 (82.1%) at the end of two months, and 27 (87.1%) patients at the end of three months. Total number of patients who relapsed (post NCT and during 3 month follow-up period) was 39 out of 63 in moxonidine group (61.9 %), and 36 out of 63 in clonidine group (57.2 %).
9 patients (14.3 %) reported dry mouth, 6 (9.5 %) reported headache and 4 (6.3 %) reported hypotension in moxonidine group whereas, 15 patients (23.8 %) reported hypotension, 12 reported (19 %) dry mouth and 11 reported dizziness (17.5 %) among clonidine group. None of the patients experienced any life-threatening side effect during the treatment. None of the side effects required cessation of the study drug and the side effects were successfully handled by minor dose adjustments.

Table 1- Comparison of sociodemographic variables between study groups

Sr. No.	VARIABLE	GROUP A (n=63)		GROUP B (n=63)		P value
		Number	Percentage	Number	Percentage	
1.	Age (yrs)					0.062
	Mean ± SD	30.35 ± 8.11		28.87 ± 5.91		
2.	Gender					-
	Male	61	96.8	61	96.8	
	Female	2	3.2	2	3.2	
3.	Marital status					0.462
	Never married	22	34.9	20	31.2	
	Married	34	54.0	38	59.4	
	Divorced	3	4.8	0	0.0	

	Widow	**1**	**1.6**	**1**	**1.6**	
	Separated due to drug abuse	**3**	**4.8**	**5**	**7.8**	
4.	**Educational status**					**0.267**
	Illiterate	**3**	**4.8**	**8**	**12.7**	
	Primary	**3**	**4.8**	**6**	**9.5**	
	Middle	**17**	**27.0**	**20**	**31.7**	
	Upto 10 and 12	**31**	**49.2**	**22**	**34.9**	
	Graduation	**9**	**14.3**	**7**	**11.1**	
5.	**Occupation**					**0.531**
	Never Employed	**3**	**4.8**	**6**	**9.5**	
	Presently unemployed	**7**	**11.1**	**9**	**14.3**	
	Full time employed	**17**	**27.0**	**19**	**29.2**	
	Self-employed	**27**	**42.9**	**25**	**39.7**	
	Student	**9**	**14.3**	**4**	**6.3**	
6.	**Family type**					**0.614**
	Joint Family	**35**	**55.6**	**35**	**55.6**	
	Nuclear Family	**24**	**38.1**	**27**	**42.9**	
	Alone	**2**	**3.2**	**0**	**0.0**	
	With Friends	**2**	**3.2**	**1**	**1.6**	
7.	**Substance of use**					**0.593**
	(Heroin, smack, brown sugar)	**56**	**88.9**	**54**	**85.7**	
	(Opium, doda, etc.)	**7**	**11.1**	**9**	**14.3**	
8.	**Route of administration**					**0.668**
	IV use	**50**	**79.4**	**48**	**76.2**	
	Others	**13**	**20.6**	**15**	**23.8**	
9.	**DAST score**					
	Mean ± SD	**7.84 ± 1.12**		**8.11 ± 1.54**		**0.154**
10.	**Severity of OUD**					**0.708**
	Moderate	**21**	**33.3**	**23**	**36.5**	
	Severe	**42**	**66.7**	**40**	**63.5**	
11.	**Complications**					
A	**HIV- Yes**	**34**	**54.0**	**39**	**61.9**	**0.366**
	No	**29**	**46.0**	**24**	**38.1**	
B	**HCV- Yes**	**40**	**63.5**	**35**	**55.6**	**0.364**
	No	**23**	**36.5**	**28**	**44.4**	
C	**HBV- Yes**	**11**	**17.4**	**9**	**14.2**	**0.625**
	No	**52**	**82.5**	**54**	**85.7**	
12.	**History of previous treatment**					**0.267**
	Yes	**37**	**58.7**	**43**	**68.3**	
	No	**26**	**41.3**	**20**	**31.7**	

Table 2- Comparison of COWS, SOWS, CGI, VAS and SF-36 at various intervals among both the groups.

Scale	Baseline	P value (between groups at baseline)	7 days	P value (between groups at 7 days)	14 days	P value (between groups at 14 days)
CGI-S						
Group A	**5.52± 0.50**	**0.595**	**4.22±0.42**	**0.830**	**2.38±0.49**	**<0.001****
Group B	**5.57± 0.50**		**4.21±0.41**		**1.25±0.44**	
CGI-I						
Group A	**-**	**-**	**3.25±0.44**	**0.008**	**1.30±0.46**	**<0.001****
Group B	**-**		**3.08±0.27**		**1.02±0.32**	
COWS						
Group A	**27.89±4.97**	**0.915**	**19.06±4.76**	**0.368**	**9.22±1.94**	**0.048***
Group B	**27.79±5.01**		**18.33±4.31**		**8.49±2.16**	
SOWS						
Group A	**27.70±4.09**	**0.998**	**18.48±4.20**	**0.756**	**9.27±2.01**	**0.042***
Group B	**27.70±4.18**		**18.70±3.79**		**8.56±1.89**	
VAS						
Group A	**7.56± 0.78**	**0.499**	**5.86±0.64**	**<0.001****	**3.21±0.65**	**<0.001****
Group B	**7.46± 0.80**		**4.59±0.87**		**2.11±0.70**	
SF-36						
Domain I						
Group A	**35.73±3.60**	**0.179**	**-**	**-**	**40.41±4.99**	**<0.001****
Group B	**34.89±3.39**				**56.17±3.29**	
Domain II						
Group A	**35.46±4.13**	**0.067**	**-**	**-**	**40.22±5.67**	**<0.001****
Group B	**34.13±3.98**				**51.29±4.97**	
Domain III						
Group A	**47.51±4.06**	**0.075**	**-**	**-**	**53.48±4.87**	**0.739**

Group B	**48.78±3.87**				**53.75±4.17**	
Domain IV						
Group A	**43.87±4.42**	**0.031**	**-**	**-**	**50.98±5.49**	**<0.001****
Group B	**42.43±2.85**				**55.68±4.56**	
Domain V						
Group A	**33.17±3.59**	**0.267**	**-**	**-**	**39.03±6.26**	**<0.001****
Group B	**32.48±3.44**				**46.16±5.34**	
Domain VI						
Group A	**26.33±3.22**	**0.945**	**-**	**-**	**32.89±4.17**	**<0.001****
Group B	**26.29±4.39**				**48.94±6.02**	
Domain VII						
Group A	**26.33±3.22**	**0.424**	**-**	**-**	**29.03±4.48**	**0.952**
Group B	**26.29±4.39**				**28.98±4.43**	
Domain VIII						
Group A	**34.02±2.43**	**0.034**	**-**	**-**	**29.06±4.40**	**<0.001****
Group B	**35.06±3.03**				**54.14±4.59**	

Within groups p values not written for sake of simplicity
p<0.05=significant (*) p<0.001=highly significant (**)

Table 3- Comparison of individual items of COWS scale at baseline, 7 days and 14 days.

COWS items		**Group A**	**Group B**	**Group A**	**Group B**	**Group A**	**Group B**
		Baseline		**7 days**		**14 days**	
1	**Mean±SD**	**1.71± 0.46**	**1.81± 0.40**	**1.38± 0.49**	**1.32± 0.47**	**0.97± 0.18**	**0.79± 0.48**
	P value	**0.211**		**0.457**		**0.005***	
2	**Mean±SD**	**1.87± 0.42**	**2.19± 0.56**	**1.32± 0.59**	**1.94± 0.25**	**0.87± 0.52**	**0.65± 0.51**
	P value	**0.001**		**<0.001**		**0.021***	
3	**Mean±SD**	**3.19± 0.59**	**2.84± 0.54**	**2.40± 0.93**	**2.51± 0.86**	**1.00± 0.31**	**0.94± 0.25**
	P value	**0.001**		**0.514**		**0.255**	
4	**Mean±SD**	**3.19± 1.48**	**3.00± 1.43**	**1.92± 0.52**	**1.71± 0.52**	**0.75± 0.67**	**0.54± 0.50**

	P value	**0.461**		**0.034**		**0.107**	
5	**Mean±SD**	**4.00± 0.00**	**3.73± 0.63**	**3.30± 0.96**	**2.40± 0.61**	**1.97± 0.18**	**1.75± 0.47**
	P value	**0.001**		**<0.001**		**0.001***	
6	**Mean±SD**	**1.95± 0.38**	**1.92± 0.27**	**1.32± 0.74**	**1.73± 0.45**	**0.90± 0.71**	**0.60± 0.58**
	P value	**0.619**		**0.001**		**0.177**	
7	**Mean±SD**	**1.40± 0.71**	**2.17± 0.61**	**1.70 ± 0.46**	**0.84± 0.60**	**0.76± 0.43**	**0.30± 0.46**
	P value	**<0.001**		**<0.001**		**<0.001****	
8	**Mean±SD**	**1.62± 0.99**	**1.65± 0.57**	**0.84± 0.81**	**0.79± 0.72**	**0.40± 0.49**	**0.27± 0.45**
	P value	**0.175**		**0.868**		**0.132**	
9	**Mean±SD**	**2.27± 0.72**	**3.02± 1.10**	**1.59± 0.8**	**1.35± 0.70**	**0.84± 0.63**	**0.44± 0.50**
	P value	**<0.001**		**0.092**		**<0.001****	
10	**Mean±SD**	**2.63± 0.94**	**2.35± 0.77**	**2.44± 0.95**	**1.75± 0.54**	**1.46± 0.53**	**0.73± 0.51**
	P value	**0.064**		**<0.001**		**<0.001****	
11	**Mean±SD**	**4.05± 1.72**	**3.11± 1.19**	**2.76± 1.89**	**1.14± 1.47**	**0.43± 1.06**	**0.00± 0.00**
	P value	**<0.001**		**<0.001**		**0.002***	
Total	**Mean±SD**	**27.89± 4.97**	**27.79± 5.01**	**19.06± 4.76**	**18.33± 4.31**	**9.22± 1.94**	**8.49± 2.16**
	P value	**0.915**		**0.368**		**0.048***	

Within groups p values not written for sake of simplicity
p<0.05=significant (*) p<0.001=highly significant (**)

Table 4- Comparison of individual items of SOWS scale at baseline, 7 days and 14 days.

SOWS Items		**Group A**	**Group B**	**Group A**	**Group B**	**Group A**	**Group B**
		Baseline		**7 days**		**14 days**	
1	**Mean± SD**	**1.89±0.60**	**1.98±0.71**	**1.40±0.66**	**1.51±0.50**	**0.78±0.46**	**0.94±0.54**
	P value		**0.441**		**0.390**		**0.092**
2	**Mean± SD**	**1.56±0.59**	**1.54±0.64**	**1.03±0.51**	**1.05±0.49**	**0.38±0.49**	**0.38±0.49**
	P value		**0.996**		**0.861**		**-**
3	**Mean± SD**	**1.60±0.61**	**1.87±0.66**	**1.13±0.55**	**1.43±0.59**	**0.84±0.51**	**0.59±0.50**
	P value		**0.021**		**0.003**		**0.008***
4	**Mean± SD**	**1.73±0.63**	**1.49±0.64**	**1.22±0.46**	**0.94±0.67**	**0.37±0.49**	**0.32±0.47**
	P value		**0.039**		**0.009**		**0.574**

5	**Mean± SD**	**1.59±0.69**	**1.56±0.67**	**1.19±0.62**	**0.87±0.61**	**0.35±0.48**	**0.17±0.38**
	P value		**0.862**		**0.005**		**0.026***
6	**Mean± SD**	**2.10±0.76**	**1.65±0.51**	**1.51±0.56**	**1.02±0.52**	**0.79±0.41**	**0.38±0.49**
	P value		**<0.001**		**<0.001**		**<0.001****
7	**Mean± SD**	**1.83±0.52**	**2.14±0.62**	**1.32±0.47**	**1.43±0.56**	**0.89±0.32**	**0.63±0.49**
	P value		**0.003**		**0.170**		**0.001***
8	**Mean± SD**	**1.89±0.51**	**1.29±0.55**	**1.16±0.45**	**0.76±0.50**	**0.37±0.49**	**0.13±0.34**
	P value		**<0.001**		**<0.001**		**0.002***
9	**Mean± SD**	**1.65±0.54**	**1.27±0.54**	**1.05±0.42**	**0.76±0.50**	**0.32±0.47**	**0.13±0.34**
	P value		**<0.001**		**0.001**		**0.010***
10	**Mean± SD**	**2.00±0.67**	**2.52±0.53**	**1.27±0.54**	**1.79±0.45**	**0.84±0.37**	**1.00±0.36**
	P value		**<0.001**		**<0.001**		**0.018***
11	**Mean± SD**	**2.19±0.64**	**2.37±0.52**	**1.54±0.53**	**1.76±0.47**	**0.97±0.18**	**1.05±0.33**
	P value		**0.146**		**0.018**		**0.096**
12	**Mean± SD**	**1.75±0.72**	**1.65±0.57**	**1.19±0.43**	**1.17±0.49**	**0.84±0.37**	**0.38±0.49**
	P value		**0.577**		**0.902**		**<0.001****
13	**Mean± SD**	**1.44±0.67**	**1.03±0.47**	**0.92±0.45**	**0.68±0.50**	**0.44±0.50**	**0.05±0.21**
	P value		**<0.001**		**0.007**		**<0.001****
14	**Mean± SD**	**1.52±0.56**	**2.02±0.61**	**1.22±034**	**1.11±0.53**	**1.00±0.36**	**0.75±0.44**
	P value		**<0.001**		**<0.001**		**0.001***
15	**Mean± SD**	**1.21±0.48**	**1.25±0.67**	**0.75±0.51**	**0.60±0.55**	**0.24±0.43**	**0.32±0.47**
	P value		**0.299**		**0.116**		**0.322**
16	**Mean± SD**	**1.76±0.64**	**2.10±0.50**	**1.29±0.54**	**1.26±0.50**	**0.87±0.46**	**0.30±0.46**
	P value		**0.001**		**<0.001**		**<0.001****
TOTAL	**Mean± SD**	**27.70±4.09**	**27.70±4.18**	**18.48±4.20**	**18.70±3.79**	**9.27±2.01**	**8.56±1.89**
	P value		**0.998**		**0.756**		**0.042***

Within groups p values not written for sake of simplicity

p<0.05=significant (*) p<0.001=highly significant (**)

Table 5- Comparison of retention rate and relapse rate on Naltrexone treatment at monthly follow-up visits for 3 months among the study groups.

	Group A (n=63)				Group B (n=63)			
	Retention		Relapse		Retention		Relapse	
	N	%	N	%	N	%	N	%
14 days	42	66.7	21	33.3	50	79.4	13	20.6
1 Month	34	80.9	8	19.1	39	78.0	11	22.0
2 Month	28	82.3	6	17.7	31	82.1	8	17.9
3 Month	24	85.7	4	14.3	27	87.1	4	12.9

Total relapses after detoxification phase till 3 months	Group A (n=63)		Group B (n=63)	
	Number 39	Percentage 61.9%	Number 36	Percentage 57.2%

Total retention after detoxification phase till 3 months	Group A (n=63)		Group B (n=63)	
	Number 24	Percentage 38.1%	Number 27	Percentage 42.8%

Discussion

Key findings: To our knowledge, the present study is the first effort to compare moxonidine and clonidine for opioid withdrawal using standardized rating scales and sound methodology. No statistically significant difference between the study groups on sociodemographic parameters reflects the similar catchment area for the groups and the sound randomization technique. The fact that more than 75% patients were iv drug users and on the younger side of age reflects that menace of opioid dependence is strangling the most productive population in the state of Punjab and serious multipronged efforts are required to tackle it at the earliest.

The major finding of the present study is that both clonidine and moxonidine are effective in treatment of opioid withdrawal symptoms in combination with buprenorphine and naloxone. However, clonidine is significantly more effective than moxonidine in treating withdrawal symptoms, craving as well as improving quality of life in short term. During withdrawal from opioids, there is rebound hyperactivity of noradrenergic (NA) system which is responsible for withdrawal symptoms like jitters, anxiety, muscle cramps, and diarrhea. Both clonidine and moxonidine are alpha 2 adrenergic receptor agonists as well as imidazoline receptor agonists, mechanisms responsible for their efficacy in treating opioid withdrawal symptoms. However, in this study, better efficacy of Clonidine could be possibly due to more specific alpha-2 adrenergic agonistic action than imidazoline agonistic action of Clonidine [7] as compared to imidazoline 1 receptor agonistic action with only minimal alpha 2 adrenergic action of Moxonidine.[6] Hence, Moxonidine being the enantiomer of Clonidine did not provide better efficacy in comparison to Clonidine in control of withdrawal symptoms in OUD. It can be attributed to the relation of withdrawal symptoms to adrenergic receptors more than imidazoline receptors. The efficacy of Clonidine in reducing withdrawal symptoms in opioid dependence is well established in previous literature and it is mentioned as a standard drug for this purpose in various guidelines.[18,19,20] A case report showed moxonidine to be beneficial in opioid withdrawal.[7]

The improvement seen in quality of life in both the groups has been seen in previous studies also which could be attributed to significant improvement in withdrawal symptoms in both the groups.[21,22] However, long term studies are required to assess if the improvement in quality of life in maintained.

The retention rates found in the present study are higher than some previous studies.[20,23] However, ours is a 3 months follow up period only as compared to previous studies which had longer follow up (6 months to 1 year). It is also observed in various studies that the risk of relapse increases with the duration of maintenance treatment due to gradual non compliance on the prescribed treatment and various psychosocial factors.[23] Thus, it is very important to retain patients in to treatment and follow up with psycho education so that long term relapse rate is minimized.

Conclusion:

In this study, it was hypothesized that Moxonidine being the enantiomer of Clonidine will have better effect in control of withdrawal symptoms in OUD patients. Therefore this non- inferiority trial was conducted to prove the same. However the study results showed superiority of clonidine over moxonidine believing it to be due to different receptor functioning.

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