ABSTRACT: AIM: The aim of the study is to compare quetiapine with placebo along with oral naltrexone in the treatment of opioid dependent patients. We conducted the study as opioid dependence is steadily increasing in this area and more research is needed to prevent relapse after opioid detoxification. SETTINGS AND DESIGN: It is a double blind placebo controlled, randomized study that was conducted in department of psychiatry, de addiction unit (Sri Guru Ram Das Institute of Medical Sciences & Research, Sri Amritsar) over one year time period. All the patients who were taken in the study had a confirmed diagnosis of opioid dependence as per ICD 10 criteria. MATERIAL AND METHOD: It is a double blind, placebo controlled, randomized study. A total of 217 subjects were admitted over year, out of which 164 were screened as 53 subjects refused to participate. Out of 164 randomization of 152 patient was done and two groups (1&2) were made. During detoxification, opioids were given to both groups and stopped after 1-2 weeks. Then all patients were started on Naltrexone 50 mg/day. Group 1 (n=73) received naltrexone (50mg/day) plus quetiapine (50-200mg/day), while group 2 (n=79) received naltrexone (50mg/day) plus placebo (multivitamin) for next 26 weeks. Our primary efficacy measures were relapse rate and percent days of abstinence. Two groups were compared with the help of percentage method and independent t test done. RESULTS: Relapse rate in placebo group was almost twice to that of Quetiapine group. In group 1, 24 subjects (32.87%) had relapsed by the end of 6 months as compared to 56 subjects (70.88%) in group 2. Percent days of abstinence in Quetiapine group were significantly higher as compared to placebo group. DISCUSSION: Our study shows significant advantages in using Quetiapine along with Naltrexone to decrease relapse rate and increase percent days of abstinence after inpatient detoxification. KEYWORDS: Opioid Dependence, Quetiapine, Naltrexone.

INTRODUCTION: Quetiapine is a second-generation antipsychotic, which is commonly used in clinical practice and is recommended by FDA for treatment of schizophrenia, acute mania, bipolar disorders, and other psychotic disorders, and is used off label for extra psychotic symptom clusters such as anxiety and insomnia. Treatment of substance dependence disorders is complex and multidisciplinary and involves efforts by the patient to maintain sobriety, structured living and attendance at self-help group meetings along with individual, group and family therapy. Pharmacotherapy might provide some benefit, but there is disagreement about the potential benefits of various pharmacologic agents for the treatment of substance dependence. The potential benefit of antipsychotic drugs for the treatment of substance use disorders has been seen in patients with schizophrenia or other psychotic illness who also reported concurrent substance dependence disorders.
Even though the medications were prescribed primarily for the treatment of the underlying psychosis, patients taking these medications reported a significant reduction in substance use. However, the evidence for the potential benefit of the antipsychotic medications in reducing substance use alone has not been consistent. Although some studies suggest that their use decreases substance use, other researchers contend that the substance use might increase with the use of typical antipsychotic medications.

A review of the literature suggests that the differences in efficacy might occur because of differences in the mechanism of action of these antipsychotic medications. Antipsychotic medications with a lower potency (such as chlorpromazine) might appear to reduce substance use, whereas those with higher potency (haloperidol) might appear to have limited benefits and perhaps may increase the substance use. The author suggested that this might occur because of the antipsychotic medications' dopamine antagonism in the mesocorticolimbic neurons of the “reward pathway.” The higher-potency antipsychotic medications exert more of this antagonistic effect, whereas those with a lower potency show less dopamine antagonism.\(^{(4)}\)

The antipsychotic medications with lower potency, such as chlorpromazine and thioridazine, have been used for the treatment of patients with substance use disorders but no psychotic disorder; however, because of the potential for adverse effects, which include tardive dyskinesia, neuroleptic malignant syndrome and extrapyramidal side effects, antipsychotic medications have never achieved widespread use in the treatment of substance use disorders. Novel antipsychotic medications show significantly less dopamine antagonism and exert their clinical effects through their actions on the serotonin, histamine and norepinephrine pathways. Clozapine, olanzapine and quetiapine are a few of the antipsychotic medications that share this mechanism of action. They might provide some benefit for patients with substance dependence because of their minimal dopamine blockade.

A study reported that in a sample of 38 patients with schizophrenia and substance dependence, 3 years of clozapine treatment decreased the cravings for alcohol and drugs by 85%.\(^{(5)}\) Another author conducted a prospective study of 151 patients with schizophrenia and substance dependence and found that 79% of patients who were prescribed clozapine achieved complete sobriety after 3 years, versus only 33% of patients taking other typical antipsychotic drugs.\(^{(6)}\)

Another study reported benefits of clozapine in decreasing substance dependence.\(^{(7)}\) Several other studies reports in the literature suggest benefits of novel antipsychotics in decreasing substance dependence in patients with a dual diagnosis (i.e. psychosis comorbid with substance abuse).\(^{(8,9,10,11,12)}\) A 12-month open-label trial of olanzapine conducted in 30 patients with schizophrenia and substance dependence found that 70% of patients achieved sobriety by the twelfth month.\(^{(13)}\)

In a study using electronic databases, relevant literature was screened including only those studies that used a randomized, double-blind, placebo-controlled or case-control design that had duration of 4 weeks or longer. A total of 43 studies were identified; of these, 23 fell into the category of Dual diagnosis (DD) and 20 into the category of single diagnosis (SD). Studies in the DD category suggested that atypical antipsychotic agents, especially clozapine, may decrease substance use in individuals with alcohol and drug (Mostly cannabis) use disorders. Studies in the SD category suggested that atypical antipsychotic agents may be beneficial for the treatment of alcohol dependence, at least in some subpopulations of alcoholics. They also suggested that these agents are not effective in treating stimulant dependence and may aggravate the condition in some cases.\(^{(14)}\)
Another study to determine whether quetiapine plus naltrexone is more effective than naltrexone alone for the treatment of alcohol-dependent patients, a double-blind, randomized clinical trial where eligible alcohol-dependent patients were randomized to receive naltrexone (50mg/day) plus quetiapine (25-200mg/day) or naltrexone (50mg/day) plus placebo for 12 weeks, and afterwards patients received naltrexone alone during 4 additional weeks, it was found that there were no statistically significant differences for any primary drinking outcomes between treatment groups. Both regimens were well tolerated. This study failed to demonstrate any additional benefit from the combination of quetiapine and naltrexone compared to naltrexone alone on drinking outcomes.\(^{(15)}\)

Total of 20 non-treatment seeking alcohol dependent individuals were randomized to one of the following conditions in a double-blind, placebo-controlled design: (1) quetiapine (400mg/day); or (2) matched placebo. Participants completed two counterbalanced intravenous placebo-alcohol administration sessions as well as behavioral measure of response inhibition (i.e. stop signal task) pre and post placebo-alcohol administration sessions. Analyses revealed a significant effect of quetiapine in improving response inhibition as measured by the stop signal task. These results provided preliminary evidence suggesting that quetiapine improves response inhibition in alcohol dependent patients, as compared to placebo.\(^{(16)}\)

A study reported that, in the treatment of patients with psychotic or bipolar disorder with a comorbid substance abuse disorder even though quetiapine was prescribed primarily for the treatment of the underlying psychotic symptoms, patients taking this medication reported a significant reduction in substance use. Also, there are case reports of quetiapine abuse and dependence; in particular among prisoners and patients diagnosed with substance abuse. This abuse of quetiapine is thought to occur due to the anxiolytic and sedative effects of the drug. There are no controlled studies on quetiapine dependence in the literature and it remains unknown whether or not quetiapine causes dependence.\(^{(17)}\)

Till now, there are no RCTs studying the role of Quetiapine in opioid craving or preventing relapse. Currently, Naltrexone is the only drug being used for relapse prevention but its role is limited by its cost and efficacy. We aim to study use of Quetiapine as an adjuvant to Naltrexone in our hospital set up as opioid dependence is steadily increasing in this area and more research is needed to prevent relapse after opioid detoxification.

**MATERIAL & METHODS:** This study was conducted in Department of Psychiatry (De-addiction unit), ShriGuru Ram Das institute of medical sciences & research, Vallah, Amritsar over one year time period (April 2014 to April 2015), after permission from Institutional Ethics Committee. All the patients with a confirmed diagnosis of opioid dependence (as per ICD -10) criteria), admitted for detoxification in the de-addiction unit were given an option to participate in this study after discharge. Average stay of subjects for detoxification varied from two to four weeks depending on withdrawal signs and symptoms. Inpatient Detoxification was done using Tramadol, Buprenorphine, NSAIDS, Benzodiazepines, Antihistamines, Clonidine, antacids, and antiemetics. Exclusion criteria included comorbid other drug addictions (Except tobacco), significant comorbid psychiatric or medical ailment, age <18 years, refusal to sign consent, and known history of any adverse reaction with Naltrexone or Quetiapine.

This was a double blind, placebo controlled, randomized study. A total of 217 subjects were admitted over year, out of which 164 were screened as 53 subjects refused to participate. During
screening, subjects received written information in vernacular language, regarding the study & explanation was done in one to one sitting for their queries about the study. A written informed consent was given for signing after it. Out of 164, 12 subjects met defined exclusion criteria and randomization of remaining 152 patients was done with the envelop method by clinician (Psychiatrist 1), that ensured approximately equal no. of patients in each group. Two groups were made (Group 1 & Group 2) as shown in chart 1. Patients in each group were compared with respect to their sociodemographic variables i.e. age, income, education, etc.

During detoxification, substitute opioids were given to both groups along with other medication and gradually tapered off and stopped after 1-2 weeks so that after 2 weeks all patients were started on Naltrexone 50mg/day. Group 1 (n=73) received naltrexone (50mg/day) plus quetiapine (50-200mg/day), while group 2 (n=79) received naltrexone (50mg/day) plus placebo (Multi-vitamin) for next 26 weeks. Dose of Quetiapine was calculated as maximum tolerated dose at determined clinically. After 26 weeks, both groups received naltrexone alone for 2 additional weeks which was then stopped.

Patients were monitored weekly initially in inpatient unit and later in outpatient unit once Naltrexone was started. Subjects as well as their attendants were not revealed regarding their group status. They were blind whether Quetiapine or multivitamin was being given along with Naltrexone. Attendants were made responsible for supervising daily medication at home and were advised to make note if they suspect the subject for any substance abuse. Clinician (Psychiatrist 2) monitoring both groups for relapse and any side effects of medication was also blind to group status of subjects. Urine for drug abuse was done at every visit to monitor relapse. Subjects and their attendants were interviewed regarding number of days of abstinence during the week and if relapsed, then type and amount of substance abused.

Any adverse effects with naltrexone and quetiapine were monitored clinically and by rating scales at every visit along with relevant blood tests, as needed clinically. Subjects, who could not complete the study due to any reason or were lost to follow up, were considered as relapse in both the groups. Their last observations were carried forward to calculate the final data rather than considering only the completed subjects to avoid the bias. This study was conducted in accordance with the ICH-GCP guidelines. Counseling of both groups for adherence to treatment therapy was done during inpatient stay by trained psychologist, who was blind to group status of subjects.

Our primary efficacy measures were relapse rate (total number of patients relapsed divided by total number of subjects in that group) and percent days of abstinence (total number of days of abstinence divided by total duration of study i.e. 182 days). Relapse was defined as subjects using any substance of abuse (except Tobacco).
Table 1

|                       | Group 1 | Group 2 | p Value | Significant Level |
|-----------------------|---------|---------|---------|-------------------|
| Age (Years)           | n=73    | n=79    |         |                   |
| Mean                  | 24.89   | 26.14   | 1.07    | NS                |
| SD                    | 6.96    | 7.42    |         |                   |
| Weight (Kg)           |         |         |         |                   |
| Mean                  | 69.00   | 70.18   | .60     | NS                |
| SD                    | 8.87    | 14.47   |         |                   |
| Height (Inches)       |         |         |         |                   |
| Mean                  | 68.55   | 69.43   | .56     | NS                |
| SD                    | 9.30    | 10.04   |         |                   |

Chart 1
RELAPSE RATE:

|                      | Group 1 (N=73) | Group 2 (N=79) |
|----------------------|----------------|----------------|
| **Sex**              | Male           | Male           |
| **Religion**         |                |                |
| Sikh                 | 37 (50.68%)    | 35 (44.30%)    |
| Hindu                | 25 (34.24%)    | 23 (29.11%)    |
| Other                | 11 (15.06%)    | 21 (26.58%)    |
| **Income (Rs /mt.)** |                |                |
| 0 - <5000            | 15 (20.54%)    | 9 (11.39%)     |
| 5000 -<10000         | 29 (39.72%)    | 31 (39.24%)    |
| 10000 -<20000        | 18 (24.65%)    | 25 (31.64%)    |
| 20000 –Above         | 11 (15.06%)    | 14 (17.72%)    |
| **Education**        |                |                |
| Illiterate           | 9 (12.32%)     | 8 (11.39%)     |
| Matric. & below      | 22 (30.13%)    | 24 (30.37%)    |
| High secondary       | 28 (38.35%)    | 39 (49.36%)    |
| Graduate & above     | 14 (19.17%)    | 18 (22.78%)    |

Table 2

p<0.05.
DISCUSSION: As evident from Table 1, sociodemographic profile of both the groups did not show any significant difference in age, weight or height. Both groups appear to be effectively randomised. Religion, income, or education does not appear to be a deterrent factor for opioid dependence as shown in Table 2. Difference between religions in both groups appears to be concordant with population distribution of different religions in this area. Opioids, despite being expensive are abused by all economic groups invariably. This may depict its ease of access and alternate source of money being used for opioid abuse, either through thefts or trafficking. Difference in education may also suggest literacy pattern of this area rather than any significant difference between groups.

Relapse rate in placebo group was almost twice to that of Quetiapine group as shown in chart 2. In group 1, 24 subjects (32.87%) had relapsed by the end of 6 months as compared to 56 subjects (70.88%) in group 2. Relapse was considered as use of any substance (except tobacco) after inpatient detoxification. This result might be significant, as till date only Naltrexone is being used to prevent relapse, with antipsychotics being used off label only. Use of Quetiapine along with Naltrexone might be more efficacious as well as more economical as lesser dose of Naltrexone would suffice. Moreover, as lesser subjects would relapse, repetitive hospitalizations would reduce, hence economic burden on family members would be less.

Percent days of abstinence in Quetiapine group were significantly higher as compared to placebo group (Chart 3). Abstinence from substances of abuse (except tobacco) was verified by interview with subject, their family attendant, and urine for drug abuse.

Number needed to treat (NNT) was also calculated for achieving complete abstinence from opioids with Quetiapine at 6 months. In group 1 and group 2, 49 & 23 subjects maintained abstinence at end point of study respectively. NNT for opioids with Quetiapine was 2.6, which is significant with respect to high relapse rate within first 6 months.

Loss to follow up rate for both the groups was found to be similar (Group 1=20.54% vs Group 2=24.05%, with group 1 showing slightly better tolerability. In group 1(Quetiapine along with Naltrexone), 15 out of 73 subjects were lost to follow up, due to any reasons which may include...
intolerability. On the other hand, Naltrexone along with placebo group had 19 subjects relapsed out of 79.

**CONCLUSION:** Our study shows significant advantages in using Quetiapine along with Naltrexone to decrease relapse rate and increase percent days of abstinence after inpatient detoxification. It also shows comparable tolerability of Quetiapine Naltrexone combination with Naltrexone alone. Quetiapine might have antagonistic effect on reward pathway of brain, and thus helpful in reducing craving.

A study found Quetiapine helpful in abating symptoms of opioid withdrawal where treatment regimen generally included clonidine, hydroxyzine, trazodone, diphenoxylate/atropine, and sometimes clordiazepoxide. Patients were instructed to take quetiapine for symptoms of withdrawal or craving. It was found that quetiapine helped reduce craving for opioids, decreased anxiety, reduced somatic pain and helped alleviate insomnia.\(^{(18)}\)

In addition to Dopamine and serotonin receptors, Quetiapine binds to histamine H\(_1\) receptors and produces sedation, which might also decrease anxiety and improve sleep. Patients with substance dependence often show fixed obsessive thinking that revolves around drugs. The antipsychotic effects of quetiapine may decrease this fixed thinking and allow patients to look beyond their substance use.

Quetiapine’s beneficial effects in decreasing substance dependence may be explained, which suggests that substances are abused to overcome anxiety or the distressing effects of illness or its treatment. However, there may also be some other, yet unexplained, mechanism that causes quetiapine to decrease substance dependence. However, there have been concerns by some researchers regarding abuse potential of Quetiapine.\(^{(19)}\)

Quetiapine’s dependence potential and abuse liability was examined through animal behavioral tests using rodents to study the mechanism of quetiapine. The results demonstrated that quetiapine affects the neurological systems related to abuse liability and has the potential to lead psychological dependence, as well.\(^{(20)}\)

It might also be interesting to compare role of Naltrexone directly with Quetiapine in reducing opioid craving. More research is needed to study the abuse liability, anti-withdrawal, and anticraving effects of Quetiapine as it can be a significant drug for acute, continuous, as well as maintenance phase of opioid detoxification, alone or along with Naltrexone.

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AUTHORS:
1. Harsh Chalana  
2. Jasmine Kaur Sachdeva  
3. TanuKundal  
4. Amandeep Singh Malhari  
5. Rajiv Choudhary

PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Psychiatry, SGRDIMSR, Amritsar. 
2. Associate Professor, Department of Medicine, SGRDIMSR, Amritsar. 
3. Senior Resident, Department of Psychiatry, SGRDIMSR, Amritsar. 
4. Clinical Psychologist, Department of Psychiatry, SGRDIMSR, Amritsar. 
5. Assistant Professor, Department of Forensic Medicine, SGRDIMSR, Amritsar.

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NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:
Harsh Chalana,  
Associate Professor,  
Department of Psychiatry,  
SGRIMSR, Amritsar. 
E-mail: harsh_chalana@yahoo.co.in

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