



## Randomized Single Blind Study of the Efficacy of Pregabalin vs. Clonidine in the Treatment of Opioid Withdrawal Syndrome: Results of Intermediate Analysis

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### Abstract

**Introduction:** Treatment of opioid withdrawal syndrome (OWS), commonly referred to as “detoxification”, is one of the most important problems in addiction psychiatry. Existing pharmacotherapy detoxification protocols are poorly tolerated and studies indicate that many of the patients do not complete treatment. Hyperalgesia, sleep disturbances and anxiety are the symptoms often cited as causes of failure to detoxify. Pregabalin (Lyrica ®) is an effective analgesic, anxiolytic and hypnotic medication. This study tested the hypothesis that Pregabalin is a safe and effective adjunct to opioid detoxification therapy.

**Methods:** Study design: Single-blind randomized symptom-regulated protocol with an active control. Thirty-four patients admitted to an inpatient addiction treatment program were randomly assigned to two groups. The first group (N=19) received up to 600 mg a day of Pregabalin for six days along with symptomatic therapy that was divided into basic treatment that was given to all patients (Doxylamin 30 mg/day) and additional medications based on patients’ needs as determined by a psychiatrist using the Opioid Withdrawal Scale and included Ketorolac, Loperamide, Metoclopramide, Nefazolin and Phenazepam (a benzodiazepine developed in Russia for sleep). The second group (N=15) received up to 600 micrograms of Clonidine a day as the main treatment along with the same basic and symptomatic regimen. No other medications were prescribed to these patients. Opiate withdrawal severity, craving, sleep disturbance, anxiety and depression, as well as general clinical impressions and side effects were assessed daily by psychiatrists who were blind to patients’ group assignment using internationally validated quantitative psychometric instruments.

**Results:** The two patient groups did not differ significantly on baseline in clinical or demographic characteristics or severity of opioid withdrawal. In the Pregabalin group, 15 out of 19 patients completed treatment (79%) compared to 7 out of 15 patients (47%) in the Clonidine group ( $p = 0,05$ ; Fisher exact test). Kaplan-Meier survival analysis also confirmed better patient retention in the Pregabalin group ( $p = 0,001$ ; Log Rank (Mantel-Cox) criterion). There were no statistically significant differences between groups on any assessments of the severity of OWS (reduction of the severity of opiate withdrawal), perhaps because of the symptom-triggered study design and small sample size. However, in the Pregabalin group there were lower indicators of the severity of craving for opiates ( $p = 0,05$ ), anxiety ( $p = 0,05$ ) and depression ( $p < 0,05$ ), while patient-rated self-assessment of their general health condition with a visual analog scale was significantly better in the Pregabalin group ( $p < 0,05$ ). An average dose of symptom-triggered ketorolac (NSAID analgesic) in the Clonidine group was almost twice that of the Pregabalin group ( $60,5 \pm 8,2\text{mg}$  vs.  $36,0 \pm 7,8\text{mg}$ ,  $p < 0,05$ ). There were no significant differences in the frequency of adverse events between the groups, however, the Pregabalin group reported less fatigue compared to the Clonidine group (16% vs. 47%,  $p < 0,05$ ). We conclude that reduced craving, fatigue and analgesic requirements in the Pregabalin patients indicate that they tolerated the withdrawal better than the clonidine comparison group, and that led to a higher detoxification completion rate (retention).

**Conclusion:** These preliminary results indicate that a Pregabalin-based opioid withdrawal protocol is likely safe and effective and results in better outcomes than the usual Clonidine-based protocol. The mechanism underlying this effect is likely related to a reduction in glutamate release from hyper-excited glutamatergic neurons which might reduce dysregulations of endogenous opioid neuropeptides.

**Keywords:** Pregabalin; Clonidine; Opioid withdrawal syndrome; Pharmacotherapy

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## Introduction

Existing abstinence oriented detoxification protocols (treatment of opioid withdrawal syndrome (OWS)) are clonidine based, poorly tolerated and many of the patients do not complete treatment [1,2]. Hyperalgesia, sleep disturbances and anxiety are the main symptoms of OWS. Pregabalin is an effective analgesic, anxiolytic and hypnotic medication. This study tested the hypothesis that Pregabalin is a safe and effective adjunct to opioid detoxification therapy.

## Methods

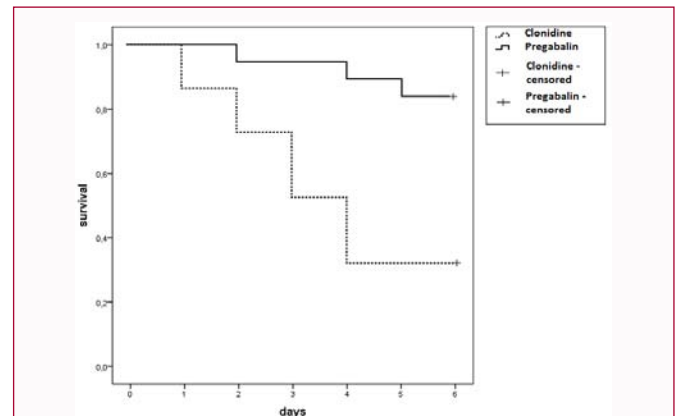
### Study design

Single-blind randomized symptom-regulated protocol with an active control. Thirty-four patients admitted to an inpatient addiction treatment program were randomly assigned to two groups. The first group (N = 19) received up to 600 mg a day of Pregabalin for six days along with symptomatic therapy that was divided into basic treatment that was given to all patients (Doxylamin 30 mg/day) and additional medications based on patients' needs as determined by a psychiatrist using the Opioid Withdrawal Scale [3] and included Ketorolac, Loperamide, Metoclopramide, Nefazolin and Phenazepam (benzodiazepine). The second group (N = 15) received up to 600 micrograms of Clonidine a day as the main treatment along with the same basic and symptomatic regimen. Opiate withdrawal severity [3,4], craving for opiates (visual analog scale), sleep disturbance, anxiety and depression [5], as well as general clinical impressions [6] and side effects were assessed daily by psychiatrists who were blind to patients' group assignment using internationally validated quantitative psychometric instruments.

## Results and Discussion

The two patient groups did not differ significantly on baseline. In the Pregabalin group, 15 out of 19 patients completed treatment (79%) compared to 7 out of 15 patients (47%) in the Clonidine group ( $p = 0.05$ ; Fisher exact test). Kaplan-Meier survival analysis (Figure 1) also confirmed better patient retention in the Pregabalin group ( $p = 0.001$ ; Log Rank (Mantel-Cox) criterion).

There were no statistically significant differences between groups on any assessments of the severity of OWS (reduction of the severity of opiate withdrawal), perhaps because of the symptom-triggered study design and small sample size. However, in the Pregabalin group there were lower indicators of the severity of craving for opiates (ANOVA, Group effect,  $p = 0.05$ ), anxiety (ANOVA, Group effect,  $p = 0.05$ ) and depression (ANOVA, Group effect,  $p < 0.05$ ), while patient-rated self-assessment of their general health condition with a visual analog scale was significantly better in the Pregabalin group (ANOVA, Group effect,  $p < 0.05$ ). An average dose of symptom-triggered ketorolac (NSAID analgesic) in the Clonidine group was almost twice that of the Pregabalin group ( $60.5 \pm 8.2\text{mg}$  vs.  $36.0 \pm 7.8\text{mg}$ ,  $p < 0.05$ ). There were no significant differences in the frequency of adverse events between the groups, however, the Pregabalin group reported less fatigue compared to the Clonidine group (16% vs. 47%,  $p < 0.05$ ). We conclude that reduced craving, fatigue and analgesic requirements in the Pregabalin patients indicate that they tolerated the withdrawal better than the clonidine comparison group, and that led to a higher detoxification completion rate (retention).



**Figure 1:** Kaplan-Meier survival analysis. Statistical significance of differences between groups:  $p = 0.001$ ; Log Rank (Mantel-Cox) criterion.

Results of this study suggest that pregabalin based opioid detoxification is effective approach to treat opioid withdrawal syndrome. These results corresponds well to the anecdotal reports of patients with opioid use disorders about their pregabalin use to self-medicate opioid withdrawal syndrome. It might be that recent reports on prgabalin abuse by opiate addicts (Schifano, 2014) do not discern pregabalin abuse and pregabalin use for self-medication of opioid withdrawal syndrome which becomes quite common.

## Conclusion

These preliminary results indicate that a Pregabalin-based opioid withdrawal protocol is likely safe and effective and results in better outcomes than the usual Clonidine-based protocol. The mechanism underlying this effect is likely related to a reduction in glutamate release from hyper-excited glutamatergic neurons which might reduce dysregulations of endogenous opioid neuropeptides.

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