Nalmefene in the treatment of pathological gambling: multicentre, double-blind, placebo-controlled study

Jon E. Grant, Brian L. Odlaug, Marc N. Potenza, Eric Hollander and Suck Won Kim

Summary
Pathological gambling is a disabling disorder experienced by about 1% of adults. We randomised 233 participants (41.6% women) 1:1 to nalmefene (20 or 40 mg) or placebo. In analyses performed using an intention-to-treat (ITT) population, nalmefene failed to show statistically significant differences from placebo on primary and secondary outcomes. Post hoc analyses of only participants who received a full titration of the medication for at least 1 week demonstrated that nalmefene 40 mg/day resulted in significantly greater reductions on the primary outcome measure. These findings suggest that medication dosing may be an important consideration in achieving symptom control.

Declaration of interest
This study was funded by Somaxon Pharmaceuticals, and M.N.P. reports financial interests in Somaxon Pharmaceuticals; he consults for and has been an advisor to Boehringer Ingelheim; has received research support from the National Institutes of Health, Veteran’s Administration, Mohegan Sun Casino, National Center for Responsible Gaming (NCRG) and Forest Pharmaceuticals. J.E.G. has received research grants from NIMH, NIDA, NCRG, Forest Pharmaceuticals and GlaxoSmithKline. E.H. has received research grants from Somaxon, Solvay and Abbott.

Method
Men and women aged 18–70 years with a primary diagnosis of pathological gambling were recruited by newspaper advertisements. A minimum score of ≥21 on the Yale–Brown Obsessive Compulsive Scale Modified for Pathological Gambling (PG–YBOCS), a minimum score of ≥5 on at least one item of the Sheehan Disability Scale (SDS) and gambling within the 1 month prior to enrolment were required. Exclusion criteria included: current Axis I disorders; current treatment for pathological gambling; and an unstable medical condition. The research was conducted at 25 out-patient centres in the USA. Each treatment centre’s institutional review board approved the study and the informed consent. After complete description of the study, participants provided written informed consent.

After screening, eligible participants entered a single-blind, placebo lead-in for 1 week. Those who maintained a PG–YBOCS ≥15 after the single-blind phase were randomised (in block sizes of eight, using computer-generated randomisation with no clinical information) to: nalmefene 20 or 40 mg/day; or placebo. Treatment was initiated at 5 mg/day nalmefene or placebo equivalent during the first week of the double-blind phase, and increased to 20 mg/day for the second week. Starting at the third week of this phase, participants randomised to nalmefene 40 mg/day were started on 40 mg/day.

The primary outcome measure was the PG–YBOCS total score. Each PG–YBOCS subscale was evaluated as a secondary efficacy measure. ‘Response’ rates were based on the total score (defined as a decrease of ≥35% PG–YBOCS at the last evaluation). Secondary outcome measures were the Gambling Symptom Assessment Scale (G–SAS) and the Sheehan Disability Scale (SDS). Safety and laboratory assessments were documented at each visit.

To detect a treatment effect, a sample of 225 will yield 80% in at least one active arm vs. placebo. Dunnett simulations were run for the 3-arm trial with each active arm given a standardised treatment effect of 0.5. All randomised participants were included in the analyses of baseline demographics and safety using an intention-to-treat (ITT) principle. Post hoc analyses included only individuals who had attained the full 20 or 40 mg/day dose for at least 1 week. All tests of hypotheses were performed using a two-sided significance level of 0.05. The statistical model for the primary variable was a linear mixed model for longitudinal data.

All statistical analyses were carried out using R for Windows (R Foundation, Vienna, Austria; http://www.r-project.org).

Results
A total of 233 participants (97 (41.6%) women; mean age 46.5 years, s.d. = 12.0) were randomly assigned to nalmefene 20 mg/day (n = 77), 40 mg/day (n = 82) or placebo (n = 74). Pre-planned statistical tests revealed no statistically significant imbalances regarding age, gender, employment, living status or PG–YBOCS total scores among treatment groups. Premature discontinuation was moderate (46%, 107/233) (Fig. DS1).

In the ITT analyses, 46.8% of participants assigned to 20 mg/day, 56.1% of those assigned to 40 mg/day and 59.5% of those taking placebo were ‘responders’ (χ² = 2.661, d.f. = 2, P = 0.264). On the PG–YBOCS, a between-group analysis failed to demonstrate superiority for nalmefene at either dose (F = 1.741, d.f. = 2, P = 0.178). Neither dose of nalmefene demonstrated statistical differences from placebo on any secondary outcome measure.
In the *post hoc* analysis, using only individuals who had a full titration of the assigned doses for at least 1 week (73% of participants assigned to nalmefene), the parameter estimates from the analysis of the mean PG–YBOCS total scores, and all secondary measures, are shown in Table 1. There were statistically significant differences between the 40 mg/day group and placebo on the PG–YBOCS total score at study end-point (t = 1.96, d.f. = 14, P = 0.035).

The incidence and severity of adverse experiences in the nalmefene group were consistent with prior studies and no unusual experiences were reported. Mean values of liver function tests remained within the normal range during the course of the study.

**Discussion**

The trial failed to find that either nalmefene 40 or 20 mg/day were superior to placebo in the treatment of pathological gambling. The ITT findings, however, included 43 participants (27% of the 159 initially assigned to nalmefene) who dropped out before receiving the target dose of nalmefene (20 or 40 mg/day). In the *post hoc* analysis, which included only individuals who received at least 1 week of target nalmefene dosing, nalmefene 40 mg/day demonstrated statistical advantage over placebo on the main outcome measure of gambling symptoms and specifically the urges associated with pathological gambling. This *post hoc* finding is consistent with the previous study that found that 25, 50 or 100 mg of nalmefene reduced pathological gambling symptoms more than placebo. The discrepancy between the efficacy outcomes of these two analyses suggests that proper dosing of nalmefene appears to be associated with symptom improvement.

Our *post hoc* analyses further support the hypothesis that pharmacological manipulation of the opiate system may target core symptoms of pathological gambling. The efficacy of opioid antagonists in the treatment of addictive disorders, including pathological gambling, has been proposed to involve opioidergic modulation of mesolimbic dopamine circuitry. Further work into defining the precise manner in which opioid antagonists mediate their beneficial effects, and which people will benefit most from these drugs, could enhance treatment for pathological gambling and other impulse control disorders. The high drop out from this study raises the question of whether nalmefene is pharmacologically aversive in this group. This seems unlikely given that none of the participants' gambling symptoms worsened during the study, and the drop-out rate is consistent with that reported in pathological gambling studies of cognitive–behavioural therapy (up to 52%).

This study has limitations. First, nalmefene only demonstrated superiority in the *post hoc* analysis of a subset of participants. Use of this more selective subsample for the efficacy analysis makes it very likely that efficacy was overestimated. Given the modest efficacy demonstrated even with this manipulation of the data, it seems likely that nalmefene in either dose failed to separate from placebo using a more conventional ITT approach. Second, pathological gambling may require long-term therapy. Third, the large number of trial centres (n = 25) may have affected the trial outcome. Finally, we enrolled only individuals without current comorbidities who were seeking pharmacological treatment, not psychotherapy.

Our *post hoc* analyses suggest that nalmefene 40 mg/day may be effective in the acute treatment of pathological gambling. As effective treatments for pathological gambling emerge, it becomes increasingly important that physicians and mental healthcare providers screen for it in order to provide timely treatment.

**Table 1** Parameter estimates for primary and secondary efficacy measures for the *post hoc* analyses

<table>
<thead>
<tr>
<th>Efficacy measure</th>
<th>At baseline</th>
<th>At week 3a</th>
<th>Weekly decrease in LOGb</th>
<th>Effect size, t-test with d.f. = 14</th>
<th>At final visit, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PG–YBOCS, total score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (n = 71)</td>
<td>21.98</td>
<td>16.53</td>
<td>−6.83</td>
<td>11.29–12.26</td>
<td></td>
</tr>
<tr>
<td>20 mg/day (n = 59)</td>
<td>21.17</td>
<td>16.18</td>
<td>−6.26</td>
<td>0.49</td>
<td>11.34–12.30</td>
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<tr>
<td>40 mg/day (n = 57)</td>
<td>20.75</td>
<td>13.22</td>
<td>−9.13</td>
<td>−1.96*</td>
<td>6.06–7.21</td>
</tr>
<tr>
<td>PG–YBOCS, urge/ thought subscale</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (n = 71)</td>
<td>11.33</td>
<td>8.61</td>
<td>−3.36</td>
<td>6.01–6.48</td>
<td></td>
</tr>
<tr>
<td>20 mg/day (n = 59)</td>
<td>10.83</td>
<td>8.24</td>
<td>−2.33</td>
<td>0.22</td>
<td>5.74–6.22</td>
</tr>
<tr>
<td>40 mg/day (n = 57)</td>
<td>11.09</td>
<td>7.48</td>
<td>−4.62</td>
<td>−2.11*</td>
<td>4.04–6.41</td>
</tr>
<tr>
<td>GSAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (n = 71)</td>
<td>30.12</td>
<td>24.69</td>
<td>−6.84</td>
<td>18.93–20.55</td>
<td></td>
</tr>
<tr>
<td>20 mg/day (n = 59)</td>
<td>28.89</td>
<td>24.00</td>
<td>−6.14</td>
<td>0.52</td>
<td>19.11–20.32</td>
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<tr>
<td>40 mg/day (n = 57)</td>
<td>28.24</td>
<td>21.56</td>
<td>−6.60</td>
<td>−1.28</td>
<td>14.98–16.44</td>
</tr>
</tbody>
</table>

PG–YBOCS, Pathological Gambling Modification of the Yale–Brown Obsessive Compulsive Scale; GSAS, Gambling Symptom Assessment Scale.

a. Week 3 is when both nalmefene groups received full titration of dose for at least 1 week in the *post hoc* analyses. The natural log of visit number used in analysis. This is a non-linear function of change in efficacy measure over time.

b. Natural log of visit number used in analysis. This is a non-linear function of change in efficacy measure over time.

**References**


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Randomly assigned
\[n = 233\]

- **Placebo**
  \[n = 74\]
  - Did not complete study
    \[n = 28\]
    - Reasons:
      - Adverse event: 7
      - Protocol violation: 2
      - Withdraw from study: 8
      - Lost to follow-up: 7
      - Lack of efficacy: 2
      - Other: 2
  - Completed
    \[n = 46\]
    \[(46/74) = 62.2\%\]

- **Nalmefene 20 mg/day**
  \[n = 77\]
  - Placebo responder
    \[n = 2\]
  - Received full titration and returned for at least one visit
    \[n = 59\]
  - Did not complete study
    \[n = 15\]
    - Reasons:
      - Adverse event: 8
      - Protocol violation: 2
      - Withdraw from study: 4
      - Lost to follow-up: 3
      - Lack of efficacy: 0
      - Other: 0
  - Completed
    \[n = 44\]
    \[(44/77) = 57.1\%\]

- **Nalmefene 40 mg/day**
  \[n = 82\]
  - Placebo responder
    \[n = 4\]
  - Received full titration and returned for at least one visit
    \[n = 57\]
  - Did not complete study
    \[n = 21\]
    - Reasons:
      - Adverse event: 9
      - Protocol violation: 0
      - Withdraw from study: 8
      - Lost to follow-up: 4
      - Lack of efficacy: 0
      - Other: 0
  - Completed
    \[n = 36\]
    \[(36/82) = 43.9\%\]

*Fig. DS1* Flow of study participants.
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Supplementary Material
Supplementary material can be found at:
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