Prolonged release oxycodone–naloxone for treatment of severe restless legs syndrome after failure of previous treatment: a double-blind, randomised, placebo-controlled trial with an open-label extension

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Summary

Background Opioids are a potential new treatment for severe restless legs syndrome. We investigated the efficacy and safety of a fixed-dose combination of prolonged release oxycodone–naloxone for patients with severe restless legs syndrome inadequately controlled by previous, mainly dopaminergic, treatment.

Methods This multicentre study consisted of a 12-week randomised, double-blind, placebo-controlled trial and 40-week open-label extension phase done at 55 sites in Austria, Germany, Spain, and Sweden. Patients had symptoms for at least 6 months and an International RLS Study Group severity rating scale sum score of at least 15; patients with severe chronic obstructive pulmonary disease or a history of sleep apnoea syndrome were excluded. Patients were randomly assigned (1:1) to either study drug or matched placebo with a validated interactive response technology system in block sizes of four. Study drug was oxycodone 5·0 mg, naloxone 2·5 mg, twice per day, which was up-titrated according to investigator’s opinion to a maximum of oxycodone 40 mg, naloxone 20 mg, twice per day; in the extension, all patients started on oxycodone 5·0 mg, naloxone 2·5 mg, twice per day, which was up-titrated to a maximum of oxycodone 40 mg, naloxone 20 mg, twice per day. The primary outcome was mean change in severity of symptoms according to the International RLS Study Group severity rating scale sum score at 12 weeks. This study is registered with ClinicalTrials.gov (number NCT01112644) and with EudraCT (number 2009-011107-23).

Findings We screened 495 patients, of whom 306 were randomly assigned and 276 included in the primary analysis (132 to prolonged release oxycodone–naloxone vs 144 to placebo). 197 patients participated in the open-label extension. Mean International RLS Study Group rating scale sum score at randomisation was 31·6 (SD 4·5); mean change after 12 weeks was –16·5 (SD 11·3) in the prolonged release oxycodone–naloxone group and –9·4 (SD 10·9) in the placebo group (mean difference between groups at 12 weeks 8·15, 95% CI 5·46–10·85; p<0·0001). After the extension phase, mean sum score was 9·7 (SD 7·8). Treatment-related adverse events occurred in 109 of 150 (73%) patients in the prolonged release oxycodone–naloxone group and 66 of 154 (43%) in the placebo group during the double-blind phase; during the extension phase, 112 of 150 (73%) had treatment-related adverse events. Five of 306 (2%) patients had serious treatment-related adverse events when taking prolonged release oxycodone–naloxone (vomiting with concurrent duodenal ulcer, constipation, subileus, ileus, acute flank pain).

Interpretation Prolonged release oxycodone–naloxone was efficacious for short-term treatment of patients with severe restless legs syndrome inadequately controlled with previous treatment and the safety profile was as expected. Our study also provides evidence of open-label long-term efficacy of this treatment. Opioids can be used to treat patients with severe restless legs syndrome who have had no benefit with first-line drugs.

Funding Mundipharma Research.

Introduction Dopaminergic drugs are the recommended first-line treatment for patients with restless legs syndrome.1 Although initially effective, long-term dopaminergic treatment can result in loss of efficacy, difficulties with tolerability, or augmentation (worsening of symptoms after initial response to treatment),2 necessitating a change of drug regimen. The treating physician faces the difficult question of whether to use off-label drugs such as gabapentin, pregabalin, benzodiazepines, or opioids—either alone or in combination—or to increase the dose of dopaminergic drug, which can lead to augmentation. Opioids have long been used to treat patients with severe restless legs syndrome for whom other drugs have failed. They are recommended as off-label second-line treatment4 although clinical evidence of their effectiveness is scarce—efﬁcacy and safety of opioids for treatment of restless legs syndrome have been investigated in only one double-blind study and a few open-label or retrospective case series.3,4
Although opioids are usually well tolerated, bowel dysfunction can occur. However, a fixed-dose combination—prolonged release oxycodone–naloxone—improves bowel dysfunction compared with oxycodone, without compromise of analgesia in patients with pain. We investigated the efficacy and safety of prolonged release oxycodone–naloxone for treatment of patients with inadequately controlled severe restless legs syndrome who had daytime symptoms.

Methods

Study design and participants
We did this 12-week randomised, double-blind, placebo-controlled study with a subsequent 40-week open-label extension at 55 sites (hospitals and specialised private neurology practices) in Austria, Germany, Spain, and Sweden from April, 2010, to March, 2012. For the double-blind phase, we enrolled adult patients with a diagnosis of restless legs syndrome according to essential and supportive diagnostic criteria as assessed by the RLS diagnostic index (score ≥11; appendix). Patients had to have had symptoms for at least 6 months, an International RLS Study Group severity rating scale sum score of at least 15 at screening (indicative of at least moderate severity), daytime onset of symptoms before 1800 h at least 4 days per week, failed treatment of symptoms, and no regular intake of opioid-containing drugs at any time before enrolment. Lack of efficacy of previous drug treatment had to be a result of either intolerable side-effects or insufficient efficacy, according to medical history, and patient’s or investigator’s opinion. Patients were excluded if they had secondary restless legs syndrome or restless legs syndrome associated with previous or concomitant dopamine-receptor blocking drugs. Other exclusion criteria were a history or presence of sleep apnoea syndrome, narcolepsy, myoclonus epilepsy, hallucinations or psychotic episodes, acute clinical augmentation according to Max Planck Institute diagnostic criteria (appendix), treatment with naloxone or naltrexone within 30 days of study entry, and a contraindication or hypersensitivity to oxycodone, naloxone, related products, or other ingredients. We excluded patients with clinically evident respiratory disorders, clinically relevant constipation, or ileus. We also excluded those who had taken drugs likely to have affected sleep architecture or motor manifestations during sleep or other CNS depressants. Current alcohol or drug misuse, history of opioid misuse, taking an investigational drug within 30 days before study entry, serum ferritin less than 30 μg/L at screening, or taking monoamine oxidase inhibitors within 2 weeks before screening also led to exclusion. Shiftworkers were also excluded. Stable non-opioid analgesic regimens for reasons other than restless legs syndrome could be continued during the study. The appendix shows detailed inclusion and exclusion criteria.

Randomisation and masking

After assessment for eligibility, previous treatments for restless legs syndrome were tapered off. At randomisation (baseline), patients had not received any

Figure 1: Trial profile
drugs for restless legs syndrome for 7 days. Patients were randomly assigned (1:1) to either prolonged release oxycodone–naloxone or matching placebo tablets (identical in appearance, colour, and taste). We did the randomisation with a validated interactive response technology system that automates the random assignment of treatment groups to randomisation numbers by site in blocks of four. Random allocation sequences were generated by the sponsor and checked for accuracy by an unmasked statistician who had no other role in the study. During the double-blind phase, patients and all personnel involved in the conduct and interpretation of the study (including investigators, site personnel, and sponsor staff) were masked to treatment assignment. Treatment allocations were not made available until the study was completed and after final clinical database lock, except in the case of emergency (appendix).

Procedures

Efficacy and safety were assessed weekly for 4 weeks and at weeks 8 and 12. The starting dose of treatment was oxycodone 5·0 mg, naloxone 2·5 mg, twice daily, which could be up-titrated during the first 6 weeks to the best dose (maximum oxycodone 40 mg, naloxone 20 mg, twice per day) in weekly fixed, symmetrical increments—ie, both the morning and evening doses were increased by the same factor. Only investigators could decide to increase or decrease dose, for both the active drug and placebo. Treatment was maintained for a further 6 weeks and then down-titrated within 1 week to oxycodone 5·0 mg, naloxone 2·5 mg, twice per day, which was also the starting dose for open-label treatment phase.

During the 40-week extension phase, patients were assessed at 4-week intervals. Inclusion criteria for this phase were either completion of the double-blind phase or premature discontinuation because of loss of efficacy after at least 8 weeks of treatment, and no clinically significant augmentation in the double-blind phase according to Max Planck Institute diagnostic criteria.61 Titration to the best dose was permitted daily up to oxycodone 40 mg, naloxone 20 mg, twice per day.

The primary endpoint for the double-blind phase was the International RLS Study Group severity rating scale sum score, measured as change from baseline to 12 weeks. Scores range from 0 (no symptoms) to 40 (very severe symptoms). Secondary endpoints were change in international clinical impression27 severity (item 1) and assessment of therapeutic effect (item 3), RLS-6 scores48 (symptom severity at different times during day and night; data not shown), restless legs syndrome leg or arm pain score (numerical 11-point rating scale from 0–10),26 proportion of treatment responders for International RLS Study Group severity rating scale and clinical global impression-2 (change of condition). International RLS Study Group severity rating scale remitters, changes in disease-specific quality of life25 summary question 12 score, subjective sleep variables (Medical Outcomes Study sleep scale39), and incidence of augmentation.

International RLS Study Group severity rating scale response was defined as at least 50% improvement in sum score and Clinical Global Impression-2 responders were rated as “much improved” or “very much improved”. International RLS Study Group severity rating scale remitters were defined by a sum score of 0 during treatment (symptom-free) or 10 or less at the end of maintenance. Augmentation was assessed by an unmasked statistician who had no other role in the study.

Table 1: Demographic and clinical characteristics at study entry

<table>
<thead>
<tr>
<th></th>
<th>Prolonged release oxycodone–naloxone (n=132)</th>
<th>Placebo (n=144)</th>
<th>Estimated treatment difference (95% CI)*</th>
<th>p value</th>
</tr>
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<tr>
<td>At enrolment</td>
<td>28·6 (5·4)</td>
<td>27·6 (5·5)</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Baseline (after washout)</td>
<td>31·7 (4·4)</td>
<td>31·6 (4·7)</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Week 1</td>
<td>21·0 (9·8)</td>
<td>26·7 (7·2)</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Week 2</td>
<td>17·4 (9·0)</td>
<td>24·5 (8·4)</td>
<td>7·26 (5·28–9·23)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Week 3</td>
<td>15·5 (8·6)</td>
<td>23·2 (9·4)</td>
<td>8·00 (5·88–10·12)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Week 4</td>
<td>14·0 (8·3)</td>
<td>21·7 (10·2)</td>
<td>8·35 (6·10–10·61)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Week 8</td>
<td>11·6 (8·7)</td>
<td>17·2 (10·2)</td>
<td>5·67 (3·64–7·69)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Week 12</td>
<td>15·1 (10·6)</td>
<td>22·1 (12·2)</td>
<td>7·15 (5·46–8·85)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Week 12 (per protocol population)</td>
<td>12·4 (9·5)</td>
<td>18·0 (12·3)</td>
<td>6·35 (3·13–9·57)</td>
<td>&lt;0·0001</td>
</tr>
</tbody>
</table>

*Assessed by mixed-model repeated measures analysis. Data are as observed except for week 12, which includes early discontinuation data.
throughout the study with a prospective, standardised stepwise evaluation procedure: patients who reported worsening disease during the visits were assessed by local investigators for augmentation with the Max Planck Institute diagnostic criteria.\(^\text{16}\) Suspected augmentation led to assessment with the augmentation severity rating scale,\(^\text{22}\) and the patient was interviewed by telephone by an augmentation expert in the same country. Finally, each suspected case was assessed and categorised by an independent international augmentation expert (RPA).

We also assessed adverse events, premature study discontinuation because of adverse events, changes in clinical laboratory parameters, vital signs, 12-lead electrocardiogram, physical examinations, and clinical global impression-4 score (side-effect assessment; data not shown).

**Statistical analysis**

We estimated that a sample size of 133 patients per treatment group would provide an overall power of at least 90% at a two-sided significance level of 0.05 to detect a difference of four points on the International RLS Study Group severity rating scale sum score, assuming an SD of 10.

All statistical analyses were done with SAS (version 9.2). The appendix shows the different analyses populations. The full analysis population was defined as a modified intent-to-treat population including all randomly assigned patients who received at least one dose of study drug during the double-blind phase and who had at least 1 week of double-blind assessment for the primary outcome, in accordance with the European Medicines Agency regulation ICH-E9.\(^\text{23}\)

We compared treatment groups by mixed-model repeated measures ANCOVA.\(^\text{24,25}\) The model accounted for fixed-factor treatment by visit interaction, baseline International RLS Study Group severity rating scale sum score as a fixed covariate, and centre and patient as random-effect variables. Patients who discontinued early because of insufficient efficacy or augmentation were included in the analysis at week 12. We did a pre-specified sensitivity analysis for the primary endpoint for the per-protocol population and a post-hoc analysis for the safety population.

We tested the primary outcome at 12 weeks and then, if the difference was significant, we tested at weeks 8, 4, 3, and 2 as long as the previous assessment showed a significant difference. These assessments were done with an intersection-union test\(^\text{26}\) across the various visit outcomes, ensuring a multiple 5% significance level.

We analysed all secondary variables in an exploratory manner with the last observation carried forward.\(^\text{27}\) We compared the number of premature withdrawals, proportions of International RLS Study Group severity rating scale and clinical global impression-2 responders, and International RLS Study Group severity rating scale remitters with Fisher’s exact test; all other scores were evaluated by ANCOVA. We analysed safety descriptively and included all enrolled patients who received study medication. Adverse events were encoded with the Medical Dictionary for Regulatory Activities (version 12.1).

Analysis of the extension phase was descriptive and included all patients given study drug; for each visit we analysed all patients with data available for that visit.

This study is registered with ClinicalTrials.gov (number NCT01112644) and with EudraCT (number 2009-011107-23).

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**Figure 2: Changes in mean IRLS sum score**

Over the 12-week double-blind study period (A; full analysis population including at week 12 patients who discontinued early because of lack of therapeutic effect or augmentation). During the 40-week open-label extension (B), from end of randomised controlled phase (week 0); open-label treatment started at week 1. IRLS=International Restless Legs Syndrome Study Group severity rating scale.
Role of the funding source
The sponsor proposed the idea for this study and discussed the idea with CT, MH, BB, KR, and AO (on behalf of the sponsor) together with RK, HB, and CT designed the study and worked on all aspects including data interpretation. The study was monitored by the sponsor and the contract research organisation RPS Research Germany (Nuremberg, Germany). Data were collected by the investigators, managed by the contract research organisation, analysed by the sponsor, fully disclosed to the authors, and interpreted by the authors. The authors had full access to all the data. The article was prepared by the authors with the support of a medical writer (paid for by the sponsor). CT, RK, LG, MH, BB prepared several drafts reviewed by all coauthors and received their approval of a final version for submission.

Results
We screened 495 patients, of whom 306 were enrolled and randomly assigned (figure 1). The double-blind safety population consisted of 304 patients (mean age 62.4 years, SD 11.2; 150 assigned to prolonged release oxycodone–naloxone, 154 assigned to placebo. 204 (67%) of these patients completed 12 weeks of treatment, with discontinuation more common in the placebo group than in the prolonged release oxycodone–naloxone group (57/154 [37%] vs 43/150 [29%]). The efficacy analysis included 132 patients assigned to prolonged release oxycodone–naloxone and 144 assigned to placebo (appendix). Patient characteristics at study entry were much the same in each group (table 1).

Mean daily drug doses during the double-blind phase were oxycodone 21.9 mg (SD 15.0 mg), naloxone 11.0 mg (7.5) for a median of 91 days (IQR 36–92) and 34.4 mg (19.4 mg) of oxycodone equivalent for a median of 68 days (28–92) for placebo (safety population). Ten of 150 (7%) patients in the prolonged release oxycodone–naloxone group versus 46 of 154 (30%) patients in the placebo group received the highest daily dose of 80 mg per 24 h during the double-blind phase. Discontinuation in the double-blind phase because of tolerability problems as the primary reason occurred in 20 of 150 (13%) patients in the prolonged release oxycodone–naloxone group and ten of 154 (7%) in the placebo group; ten of 150 (7%; prolonged release oxycodone–naloxone group) and 30 of 154 (20%; placebo group) withdrew because of lack of efficacy.

Of the 197 patients included in the open-label extension, 157 (80%) completed 40 weeks of treatment (figure 1). Extension was discontinued prematurely by 16 (16%) patients who had taken prolonged release oxycodone–naloxone versus 24 (25%) who had taken placebo, mainly because of adverse events (10/101 [10%] vs 11/96 [11%]) and patient’s choice (3/101 [3%] vs 8/96 [8%]). Demographic characteristics of the extension study population were much the same as the double-blind population (appendix). Patients received a mean daily prolonged release oxycodone–naloxone dose of oxycodone 18.1 mg (SD 10.5 mg), naloxone 9.1 mg (5.3) for a median of 281 days (IQR 278–283).

Mean duration of symptoms at enrolment was 10.3 years (SD 10.0); 288 of 304 (95%) patients had restless legs syndrome for more than 1 year, with 192 of 304 (63%) having had the disease for more than 5 years. Drug treatment for restless legs syndrome was taken before the study for a mean of 5 years (SD 4.2) with 257 of 303 (85%) patients receiving treatment for at least 3 years (table 2).
least 1 year (data unavailable for one patient). All patients had had at least one previous treatment for restless legs syndrome (range 1–3).

Mean International RLS Study Group severity rating scale sum score at randomisation was 31·6 (SD 4·5). Effects of prolonged release oxycodone–naloxone were noted after 1 week (table 2, figure 2A). The change in International RLS Study Group severity rating scale sum score at 12 weeks was significantly greater for prolonged release oxycodone–naloxone (−16·6) than for placebo (−9·5) in the full analysis population (difference at 12 weeks 8·15, 95% CI 5·46–10·85; p<0.0001). Mean changes of the score were much the same for treatment weeks 2, 3, 4, and 8 (table 2) and based on a post-hoc analysis of the safety population (7·03, 95% CI 4·36–9·70; p<0.0001). A beneficial effect of treatment with prolonged release oxycodone–naloxone continued throughout the extension phase, with a mean sum score of 15·4 (11–2) at the start compared with 9·7 (SD 7·8) at week 40 (n=152; change 5·7; figure 2B).

At the end of 12 treatment weeks, more than half of all patients treated with prolonged release oxycodone–naloxone versus less than a third taking placebo were International RLS Study Group severity rating scale responders (75/132 [57%] vs 45/144 [31%]; p<0.0001). Twice as many patients in the prolonged release oxycodone–naloxone group were Clinical Global Impression-2 responders than in the placebo group (88/132 [67%] vs 50/144 [35%]; p<0.0001). During the double-blind phase, significantly more patients in the prolonged release oxycodone–naloxone group than in the placebo group were International RLS Study Group severity rating scale remitters (55/132 [42%] vs 28/144 [19%]; p<0.0001). At the end of the extension phase, 85 of 197 (43%) patients were classified as International RLS Study Group severity rating scale remitters and 43 of 197 (22%) of those patients had no symptoms. Furthermore, prolonged release oxycodone–naloxone was superior to placebo for some but not all additional efficacy, sleep, and quality of life parameters at the end of the double-blind phase; all endpoints were also improved at the end of the extension phase compared with the start but these differences were not tested statistically (table 3).

During both phases, 63 patients who reported worsening symptoms were assessed for potential augmentation; only one patient (in the prolonged release oxycodone–naloxone group) was deemed a potential case. A review of this patient by a national and an international augmentation expert (RPA) concluded that this patient did not have augmentation.

During the double-blind phase, adverse events were reported by 126 of 150 (84%) patients in the prolonged release oxycodone–naloxone group (109/150 [73%] related to treatment) versus 106 of 154 (69%) in the placebo group (66/154 [43%] related to treatment). 150 of 197 (76%) patients who started the extension phase had adverse events (112/197 [57%] were related to treatment). Table 4 shows data for safety. Consistent with the safety profile of opioids,24 treatment-related gastrointestinal disorders, nervous system disorders, fatigue, and pruritus were more common in the prolonged release oxycodone–naloxone group than in the placebo group. 12 (8%) of 150 patients had clinically relevant constipation as an adverse event during the double-blind phase. Three patients in the prolonged release oxycodone–naloxone group during the double-blind phase and three during the extension phase had serious treatment-related adverse events (table 4).

Following ethics committee advice, a follow-up visit occurred 4 weeks after the end of the open-label extension to assess symptoms of physical and psychological dependence (176 patients were reassessed). Drug withdrawal symptoms occurred in one patient after 12 weeks and two patients after 1 year of treatment. In the double-blind phase, a higher proportion of patients discontinued prematurely because of adverse events in the prolonged release oxycodone–naloxone group than in the placebo group (22/150 [15%] vs 10/154 [7%]). During the extension phase 18 of 197 (9%) discontinued prematurely.

**Discussion**

Our findings show a significant and sustained treatment effect of prolonged release oxycodone–naloxone for patients with severe restless legs syndrome insufficiently treated with first-line drugs. The 16·6 point reduction on
the International RLS Study Group severity rating scale during the double-blind phase translates into a significant clinical improvement from “very severe” at start of treatment to on average “mild” or “moderate” at the end of the double-blind phase. At the end of the extension phase, 85 of 197 (43%) patients were considered remitters. This alleviation of symptoms also led to significant improvements in some secondary objectives such as subjective quality of sleep and quality of life during the double-blind phase and showed evidence of improvement in the extension phase. Thus, prolonged release oxycodone–naloxone might in future be a clinically useful treatment for patients with severe restless legs syndrome when first-line treatment options have failed (panel).

Most patients in the prolonged release oxycodone–naloxone group had an at least 50% improvement in International RLS Study Group severity rating scale score at end of the double-blind phase and 42% had an International RLS Study Group severity rating scale sum score of 10 or less, indicating only mild symptoms. Prolonged release oxycodone–naloxone had significantly greater efficacy than did placebo despite evidence of improvements in the placebo group, which was to be expected on the basis of results from previous studies. The primary analysis was confirmed by a sensitivity analysis of different study populations, which did not show any substantial differences to the primary analysis. The treatment effect of prolonged release oxycodone–naloxone was similar or greater than that reported in previous studies of dopaminergic drugs for moderate-to-severe restless legs syndrome, although baseline severity of restless legs syndrome differed in these studies (Scholz and colleagues mean change of International RLS Study Group severity rating scale sum score 5·7, 95% CI 4·7–6·7; Hornyak and colleagues mean change of International RLS Study Group severity rating scale sum score 5·5, 95% CI 4·5–6·4).

For withdrawal because of tolerability or lack of efficacy, similar proportions to those in our study have been reported for dopaminergic first-line treatment of restless legs syndrome in prospective 1-year open-label studies for ropinirole (tolerability problems 8%, lack of efficacy 4%) and rotigotine (tolerability problems 17%, lack of efficacy 3%). Tolerability problems were more common in the latter study, because of skin reactions caused by the rotigotine patch. Generally, dropout during the double-blind phase was high and could introduce bias to our assessment of efficacy. However, high dropout is common in studies of restless legs syndrome both in study drug and placebo groups. In our study, we included severely affected patients with a history of unsuccessful treatment, for whom a 12-week treatment with placebo or insufficient dose of opioid was almost intolerable. We controlled for the potential bias in patients who discontinued prematurely by several sensitivity analyses of different study populations, which did not show any substantial differences to the primary analysis for comparisons of prolonged release oxycodone–naloxone and placebo.

Augmentation is the main and most relevant long-term complication of dopaminergic treatment for restless legs syndrome and has a large effect on quality of life. The five basic features of augmentation are shorter time to onset of symptoms, shorter latency to symptom onset at rest, increase of intensity of symptoms, shorter period of relief after taking drug treatment, and spread of symptoms to previously unaffected parts of the body. Exactly how common augmentation is with dopaminergic treatment is unknown. Long-term studies (at least 6 months) have used the National Institutes of Health

Panel: Research in context

Systematic review
We searched Medline, CINAHL, ClinicalTrials.gov, abstracts from key 2010 and 2011 scientific meetings, and drug company websites with the terms “RLS”, “trials”, “therapy”, and “augmentation” for publications published in any language between 1960, and May 31, 2013. We also identified previous double-blind, randomised, placebo-controlled and active-controlled trials from a Cochrane systematic review of efficacy and safety of dopamine agonists and meta-analyses of the efficacy and safety of dopaminergic and non-dopaminergic drugs for restless legs syndrome. We also searched the reference lists of other relevant publications, including recent guidelines for opioid treatment of restless legs syndrome. 

Interpretation
Dopaminergic medications and—to a lesser extent—calcium-channel ligands have been extensively assessed in large studies for treatment of restless legs syndrome. Opioids have been investigated in only small, mainly exploratory studies (table S). Only one double-blind, randomised crossover-study has been done—in which oxycodone was superior to placebo, with polysomnography as the primary outcome—that could demonstrate the potential of the use of opioids for restless legs syndrome. All other published opioid studies were retrospective analyses of databases and case series or case studies with a low level of evidence. Results of two studies show that opioids were mainly prescribed to patients who had failed treatments with mostly dopaminergic drugs—as per the inclusion criteria of our trial. Additionally, a case series from three large hospitals in the USA and Europe described patients treated for several years with various opioids. The investigators of that series also assessed combination treatment with opioids for 77 patients (data not shown). Further small case studies with one to seven patients have been done with intrathecal morphine. In summary, empirical evidence for the effectiveness of opioids for treatment of restless legs syndrome was insufficient until now. Our findings suggest a new, much needed, option for management of severe restless legs syndrome for patients who cannot tolerate dopaminergic drugs or for whom these drugs had loss (tolerance, augmentation) or absence (non-response) of efficacy.
We included only patients with previous failure of treatment (mostly dopaminergic). Thus, prolonged release oxycodone–naloxone was assessed only for second-line treatment and we cannot presume that it is equally as efficacious for first-line treatment, which warrants further investigation. Furthermore, we could not obtain a totally reliable and sufficiently detailed treatment and dose history to define treatment failure by an exact number of drugs and maximum doses. To date, no method to assess augmentation has been validated: in previous studies, methods to assess augmentation were retrospective. Some patients with augmentation could have been included in our study or might have been overlooked during treatment: validation of assessment methods is urgently needed. However, we did show for the first time that augmentation was not a major long-term complication of management of restless legs syndrome with prolonged release oxycodone–naloxone. Future comparative studies of dopaminergic drugs might even show a long-term benefit of prolonged release oxycodone–naloxone for treatment of severe restless legs syndrome.

**Contributors**

CT, MH, BB, AO, and KR conceived and designed the study. RK designed the study and gave scientific and operational advice during the study. CT was the principal study investigator. CT, BH, LG, DGB, and BH collected data. BB did the statistical analysis. RPA was the independent augmentation expert, JW was the national augmentation expert for Germany. All authors interpreted data and critically reviewed the report. All approved the final version of the report.

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Conflicts of interest
CT is a consultant for UCB, Vifor, Mundipharma, Britannia, Novartis,
Confl icts of interest
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support from UCB and Pfi zer consultant for UCB, Xenoport, Otsuka, and Impax, has received
consulting, or for serving on advisory boards for UCB, Boehringer
from UCB and Otsuka. BH has received honoraria for speaking,
consulting, or for serving on advisory boards for UCB, Boehringer
Ingelheim, and Mundipharma; travel support from Habel Medizintechnik Vienna and
Vivisol; and research support from UCB. MH, BB, AO and KR are
employees of Mundipharma. JW has received honoraria for speaking or
serving on advisory boards for Mundipharma, UCB, and Vifor. RPA is a consultant for GlaxoSmith Kline, Pharmacosmos, UCB, Impax, and
Pfizer. RK has received honoraria for serving on advisory boards for
UCB, Pfizer, and Mundipharma.

Acknowledgments
We thank all patients and investigators involved in this study. Writing
assistance (funded by Mundipharma Research) was provided by
Elke Grosselindemann and Birgit Brett. Publication management was
undertaken by Yvonne von Coburg (Mundipharma Research).

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