New Medicine Assessment

Oxycodone hydrochloride / naloxone hydrochloride prolonged release tablets (Targinact®)

Second line symptomatic treatment of patients with severe to very severe idiopathic restless legs syndrome

Recommendation: Black

Oxycodone hydrochloride/naloxone hydrochloride prolonged release tablets are not recommended for use as symptomatic treatment of patients with restless legs syndrome. Efficacy and safety data in support of Targinact® was not sufficient to allay concerns regarding;

- Safety issues and side effects associated with long term use of opioids
- The controlled drug status and potential for opioid abuse
- A lack of evidence for use beyond 1 year, uncertainty around the mechanism of action and potential for tolerance to develop when used to treat restless legs syndrome.

Summary of supporting evidence:

- The efficacy and safety of oxycodone/naloxone prolonged release tablets in the treatment of restless legs syndrome is derived from a pivotal phase III double-blind placebo-controlled clinical study (n=276 (FAS)) of 12 weeks' duration and an open-label extension study of 40 weeks' duration (n=197).

- The primary endpoint of change in IRLS Study Group severity rating scale sum score (an internationally accepted scoring system) at 12 weeks was significantly greater for the oxycodone/naloxone prolonged release treatment group (–16·6) than for the placebo group (–9·5) in the full analysis population (difference at 12 weeks 8·15, 95% CI 5·46–10·85; p<0·0001), according to the pre-defined statistical analysis.

- The minimum change in score that relates to a clinically significant change has been suggested as a difference at endpoint of 6 points or more on the IRLS scale. The 16.6 point reduction from 31.7 to 15.1, on the IRLS Study Group severity rating scale, is regarded therefore as clinically significant and translates into an improvement from "very severe" at the start of treatment to on average "moderate" or "mild" symptoms at the end of the double-blind phase. The magnitude of effect (decrease in mean IRLS of 5.9 points compared to placebo) was in line with or even slightly better than the results found in the placebo-controlled studies with dopamine agonists approved as first line treatments.

- There was a statistically significant improvement for those treated with oxycodone/naloxone prolonged release tablets compared to placebo in the following key secondary endpoints; improvement of severity of RLS in the Clinical Global Impression (CGI) severity scale; RLS-6 scores (measuring symptom severity at different times of the day and night), quality of life (QoL-RLS-Scale) and change in pain using the numeric rating scale (NRS) for RLS pain.

- 42% patients given oxycodone/naloxone prolonged release tablets during the double-blind phase were classified as remitters versus 19% for placebo ($p < 0.001$). 57% of oxycodone/naloxone prolonged release treated patients were responders versus 31% of placebo treated patients).

- 73% of the active comparator group reported adverse events related to treatment compared to 43% of patients in the placebo group.

- The most frequently reported adverse events for both the double-blind phase of the study and the extension phase included constipation; nausea; fatigue; somnolence and hyperhidrosis. During the double-blind and extension phases, 5 and 3 patients, respectively, in the oxycodone/naloxone prolonged release group had serious treatment-related adverse events.

- The incidence of augmentation was reported to be 0% throughout the entire study period of 52 weeks. Frequency of augmentation during the first year of treatment with dopaminergic drugs is reported to be between 9 and 60%.

- The extension phase of the RCT was open-label increasing the risk of bias. However different measures were put into place to minimise this risk such as placebo patients being able to enter the extension phase; a week's down-titration prior to entering the extension to prevent carry over treatment effects; continued blinding about their double-blind treatment on entering the extension phase; comparable proportions of patients from both treatment arms joining the extension phase (101/150 oxycodone/naloxone prolonged release treated patients and 96/154 placebo treated patients).

- Concerns were raised by the Netherlands Medicines Evaluation Board that the use of oxycodone/naloxone prolonged release could lead to tolerance and misuse. Following analysis of the scientific data and discussion within the Committee, the CHMP concluded that the overall risk of tolerance and misuse was considered low and therefore the benefits of treatment outweigh the risks.

- Oxycodone/naloxone prolonged release tablets are classed as a Schedule 2 controlled drug. There are concerns patients will be co-prescribed opioids for analgesia in addition to RLS.

- Annualised cost for one patient prescribed the mean daily dose of 20 mg/10 mg daily prescribed as 1 x 10 mg/5 mg oxycodone/naloxone prolonged release tablet twice daily is £550.16. Estimated number of patients across Lancashire eligible for treatment with oxycodone/naloxone prolonged release tablets is 27 – 98 patients (manufacturer's estimate is 21 patients). Total annual cost across Lancashire is £14 584 - £53 916 (manufacturer's estimate £11 553).

Details of Review

Name of medicine (generic & brand name)**:**

Oxycodone hydrochloride/naloxone hydrochloride (Targinact®)

Strength(s) and form(s):

5 mg/2.5 mg (5 mg oxycodone hydrochloride equivalent to 4.5 mg oxycodone and 2.73 mg of naloxone hydrochloride dehydrate equivalent to 2.5 mg naloxone hydrochloride and 2.25 mg naloxone) prolonged release (f/c, m/r) tablets

10 mg/5 mg (10 mg oxycodone hydrochloride equivalent to 9 mg oxycodone and 5.45 mg of naloxone hydrochloride dehydrate equivalent to 5 mg naloxone hydrochloride and 4.5 mg naloxone) prolonged release (f/c, m/r) tablets

20 mg/10 mg (20 mg oxycodone hydrochloride equivalent to 18 mg oxycodone and 10.9 mg of naloxone hydrochloride dehydrate equivalent to 10 mg naloxone hydrochloride and 9 mg naloxone) prolonged release (f/c, m/r) tablets

40 mg/20 mg (40 mg oxycodone hydrochloride equivalent to 36 mg oxycodone and 21.8 mg of naloxone hydrochloride dehydrate equivalent to 20 mg naloxone hydrochloride and 18 mg naloxone) prolonged release (f/c, m/r) tablets[1]

Dose and administration:

Initial dose of 1 x 5 mg / 2.5 mg oxycodone hydrochloride/naloxone hydrochloride tablet twice daily (12 hourly intervals) increased according to symptoms. Usual dose 10 mg/5 mg every 12 hours; max. 60 mg/30 mg daily oxycodone hydrochloride/naloxone hydrochloride tablets.[1]

Titration on a weekly basis is recommended. Symmetric administration is recommended, however, some patients may benefit from asymmetric dosing tailored to the individual patient.

BNF therapeutic class / mode of action

4 Central nervous system > 4.7 Analgesics > 4.7.2 Opioid analgesics[2]

Licensed indication(s):

Second line symptomatic treatment of patients with severe to very severe idiopathic restless legs syndrome (RLS) after failure of dopaminergic therapy.

Oxycodone hydrochloride/naloxone hydrochloride is indicated for patients suffering from RLS for at least 6 months. RLS symptoms should be present daily and during daytime (≥ 4 days/week). Oxycodone hydrochloride/naloxone hydrochloride should be used after failure of previous dopaminergic treatment, defined as inadequate initial response, a response that has become inadequate with time, occurrence of augmentation or unacceptable tolerability despite adequate doses. Previous treatment with at least one dopaminergic medicinal product should have lasted, in general, 4 weeks. A shorter period might be acceptable in cases of unacceptable

tolerability with dopaminergic therapy. Treatment of patients with RLS with oxycodone hydrochloride/naloxone hydrochloride should be under the supervision of a clinician with experience in the management of RLS.[1]
Proposed use (if different from, or in addition to, licensed indication above): n/a
Course and cost: Monthly cost of £42.32 - £253.90 (MIMS October 2015)
Current standard of care/comparator therapies: Non-pharmacological options: good sleep hygiene, avoidance of caffeine and alcohol, smoking cessation, moderate physical activity. During acute episodes: walking, stretching and massaging the affected limbs; application of heat with heat pads or a hot bath; relaxation exercises; mental alertness distraction at times of rest (for example, games or reading). Non-ergot dopamine agonists: pramipexole tablets, ropinirole tablets and rotigotine patches (all licensed for RLS. N.B. Rotigotine patches are not currently approved across Lancashire). Alpha-2-delta calcium-channel ligands: gabapentin and pregabalin (not licensed for RLS).
Relevant NICE guidance: n/a

Background and context

RLS, also known as Willis-Ekborn disease, is a common sensory motor neurological disorder which causes a characteristic, overwhelming and irresistible urge to move the limbs – usually the legs – in addition to uncomfortable, abnormal sensations which appear without any sensory stimulation.[3,4] RLS is often associated with sleep disturbance as symptoms are typically worse in the evenings. The pathophysiology of RLS is listed as being linked to dopaminergic dysfunction, reduced iron in the central nervous system (it is thought there is a defect in the metabolism of iron in the brain which is also linked to the conversion of levodopa to dopamine), genetic linkages, or alteration in neurotransmitters such as hypocretins and immune dysfunction, and inflammatory mechanisms.[5] RLS can be classified as either primary (idiopathic) RLS or secondary RLS whereby the symptoms are secondary to an underlying condition (most commonly pregnancy, iron deficiency anaemia, or stage 5 chronic kidney disease), or the use of certain drugs (for example, some antidepressants, some antipsychotics, and lithium).[4] The prevalence of idiopathic restless legs syndrome (RLS) is between 1.9 – 4.6% of adults in northern Europe. It is twice as prevalent in women as in men.[4]

For patients with mild RLS, non-pharmacological treatment options should be employed first before initiating medication. A regular sleep schedule and good sleep hygiene including avoidance of caffeine and alcohol is recommended. Stopping smoking and engaging in moderate physical activity can also be helpful. During an acute episode of RLS measures to relieve symptoms include: walking and stretching the affected limbs, application of heat with heat pads or a hot bath, relaxation exercises, mental alertness distraction at times of rest (for example, games or reading) and massaging affected limbs.[4] Secondary causes or exacerbating factors should be corrected e.g. supplementation for anaemia and other causes of deficiency; reviewing concomitant treatments which can worsen RLS (anti-depressants, antipsychotics, lithium, calcium channel blockers, metoclopramide and antihistamines); limiting other trigger factors e.g. avoiding smoking, or high intake of caffeine or alcohol in the evenings, weight reduction, reduce stress and increase exercise.

First-line pharmacological treatment of RLS is usually with a licensed non-ergot derivative dopamine agonists such as pramipexole or ropinirole tablets. Augmentation is a known complication of dopaminergic drugs - defined as an iatrogenic worsening of symptoms with one of two possible features: either a paradoxical response to medication, such that the patient becomes worse when the dose is increased and better when it is decreased, or an advance of the typical time of day when symptoms begin to two or more hours earlier than before treatment began. A definitive diagnosis of augmentation requires that the patient did initially respond to medication, the exclusion of other possible causes for a worsening of symptoms, and a consistent change in symptoms.[4,6] If augmentation develops, the causative drug should be stopped. One option is to switch to a non-dopaminergic drug such as an alpha-2-delta ligand (gabapentin or pregabalin) but it is advisable to seek specialist advice.

The National Institute for Health and Care Excellence (NICE) has not produced guidance for the management of RLS although there is a NICE Evidence Summary for the use of oxycodone/naloxone in RLS currently in development and due to be published in December 2015. Other relevant guidelines which have been published include the long-term treatment of RLS/Willis-Ekborn disease: evidence-based guidelines and clinical consensus best practice guidance: a report from the International RLS Study Group from 2013;[7] the European Guidelines on Management of RLS: report of a joint task force by the European Federation of Neurological Societies, the European Neurological Society and the European Sleep Research Society, updated in 2012.[8] In addition the RLS Foundation published guidance on the diagnosis and treatment in primary care of RLS in 2008.[6]

The International RLS Study Group produced evidence-based and consensus-based recommendations in 2013 based on the review of 61 papers which satisfied the inclusion criteria.[7] The group concluded: pregabalin has been established as effective for up to 1 year in treating RLS (Level A evidence – see appendix 3); pramipexole, ropinirole, and rotigotine have been established as effective for up to 6 months in treating RLS (Level A). The following drugs have been established as probably effective (Level B) in treating RLS for longer durations ranging from 1 to 5 years - pramipexole, and ropinirole (1 year); levodopa (2 years); and rotigotine (5 years). Due to the associated safety concerns, pergolide and cabergoline should not be used in the treatment of RLS unless the benefits clearly outweigh the risks in those whose symptoms are

refractory to all other treatments. Other pharmacologic therapies have insufficient evidence to support their long-term use in treating RLS. Of note, there was insufficient evidence to make a recommendation on the use of gabapentin in the long-term treatment of RLS.

The 2012 European Guidelines[8] provide evidence-based recommendations mainly for the treatment of primary RLS. These state that dopaminergic drugs are the class of drugs for which the most studies have been published since the original 2005 guidelines. Pramipexole is considered effective in the short-term for primary RLS and possibly effective for long-term treatment. Ropinirole is effective for primary RLS in the short-term and possibly long-term and finally rotigotine patches are effective for the short and long-term treatment of RLS. The ergot derivatives, cabergoline (not licensed for RLS in the UK) and lisuride (not available in the UK) are not recommended due to the potential for augmentation and negative side-effect profile – particularly the potential to induce fibrosis which requires cardiopulmonary monitoring. Levodopa has been shown to be effective but given the risk of augmentation the guidance recommends that it is not given at a dose higher than 200 mg. The guidance states that in clinical practice, levodopa is now better established as a diagnostic test and an on-demand treatment for sporadic RLS. Antiepileptic drugs also have a relatively large amount of evidence available. The guidelines state that gabapentin and pregabalin can be considered to be effective for short-term treatment of primary RLS. There is insufficient evidence to conclude on the efficacy of oxcarbazepine and lamotrigine. Previous recommendations for adrenergic agents, benzodiazepines/hypnotics and opioids remain unchanged from the original guidelines produced in 2005, due to the lack of new studies. The recommendations in the original European guidelines state the following[9]: clonidine is probably effective in reducing symptoms and sleep latency in primary RLS in the short-term though it had several side-effects which patients were able to tolerate; clonazepam should be considered as probably effective for improving symptoms in primary RLS when given at 1 mg before bedtime, but also probably ineffective when given at four doses throughout the day; for primary RLS, oxycodone at a mean dosage of 11.4 mg can be considered as probably effective in improving RLS symptoms (only level B evidence) and there is insufficient evidence to make a recommendation about morphine, tramadol, codeine and dihydrocodeine, tilidine, and methadone and about the intrathecal route of administration. Finally the updated guidelines state that whilst there is evidence that patients with low ferritin levels benefit most from iron supplementation, it remains controversial whether patients with normal ferritin levels benefit to the same degree. The recent guidance recommends that oral ferrous sulphate is considered possibly effective for the short-term treatment of primary RLS. N.B. Some of the discussed medicines may not be readily available in the UK and not all are recommended for use for the treatment of RLS in the UK. Please see LMMG RLS guidelines for local recommendations.

The 2008 RLS Foundation guidelines for the diagnosis and treatment of RLS in primary care state that dopaminergic agents are increasingly recognised as the mainstay of pharmacological therapy. These guidelines state that opioids often provide significant relief from RLS when other treatment options have failed and may also represent the optimum treatment for some patients. They note the relatively few published studies for the use of opioids in RLS and highlight concerns about their abuse potential and addiction in addition to the practical problems with prescribing “controlled” drugs. The guidance pre-dates some of the more recent trials involving pregabalin.

The guidance states that gabapentin may be particularly well suited for individuals with co-morbid RLS and peripheral neuropathy and is often used as an adjunctive agent in patients with persistent sleep disturbance due to its mild sedative properties. Finally these guidelines note that the development of dopaminergic agents with improved symptom relief have relegated benzodiazepines to second-line status or when insomnia persists after elimination of RLS symptoms.[6]

Oxycodone/naloxone prolonged release tablets consist of oxycodone, an opioid analgesic in combination with naloxone, an opioid antagonist, added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut.[1] In addition to being indicated for severe pain, which can be adequately managed only with opioid analgesics it has recently received a license for the second line symptomatic treatment of patients with severe to very severe idiopathic RLS after failure of dopaminergic therapy.

The International Restless Legs Syndrome (IRLS) Severity Scale (see Appendix 2) is an internationally accepted subjective scoring system which measures RLS symptoms using a set of 10 questions based largely on features of RLS as defined by the International Restless Legs Syndrome Study Group.[10,11] It uses a 5-point scale e.g. 0 = symptoms not present, whereas 4 = very severe intensity. The total score is the sum of the scores of the 10 items. This can range from 0 = non-RLS to 40 = very severe RLS. The authors proposed the following categories of RLS based on a patient's score: 0 = non-RLS; 1-10 = mild RLS; 11-20 = moderate RLS; 21-30 = severe RLS; 31-40 = very severe RLS. The minimum change in scale score that translates to clinically significant improvement in patients has been suggested as a difference at endpoint of 6 points or more on the IRLS scale.[12] However it needs to be noted that a recent meta-analyses showed a high sensitivity of the IRLS total score and the CGI for placebo effect.[12]

The Clinical Global Impression (CGI) Scale is also a subjective scale and is not specific for RLS, originally being developed for mental health; nevertheless it has been used to assess severity of RLS symptoms. It has 3 sections: (1) Severity of illness (2) Global improvement (CGII) or change (CGIC), and (3) Efficacy index. There are 7 categories of answers ranging from "very much improved" to "very much worse".[13]

Summary of evidence

Summary of efficacy data in proposed use:

The pivotal phase III study (see Appendix 1) was a 12 week randomised double-blind, double-dummy, placebo-controlled trial.[14] This consisted of a pre-randomisation phase that included 7day wash-out from previous therapies; followed by a double-blind phase which compared the use of oxycodone/naloxone prolonged release tablets, at initially 5/2.5 mg twice daily, versus placebo in 306 patients. The study medication dose could be titrated each week to the "best" dose, up to a maximum of oxycodone/naloxone prolonged release 40/20 mg twice daily. This is the same as the licensed dosing schedule except the maximum licensed dose is 60/30 mg daily.

Treatment was then maintained for a further 6 weeks and then down-titrated within one week to oxycodone/naloxone 5/2.5 mg twice daily. This was the starting dose for the 40 week extension open-label phase which followed this. Patients had to have at least moderate idiopathic RLS (IRLS score ≥ 15) at screening despite current or previous treatment. It is of note that patients included in the study had RLS symptoms for on average more than 10 years, with only 5% suffering from RLS symptoms for less than 1 year. The majority of patients were on dopaminergic treatment at the start of the study. The average duration of the last treatment before study entry was 25 months.[15] Patients excluded from this study were those with secondary RLS and patients taking or having taken drugs likely to affect sleep architecture or motor manifestations during sleep or other CNS depressants (see appendix 1 for full exclusion criteria). Patients showing any signs of acute augmentation during screening for the study were not included in the trial.

The mean IRLS Study Group severity rating scale sum score at randomisation for oxycodone/naloxone prolonged release was 31.7 (SD 4.4) and this was reduced to 15.1 (SD 10.6) at the end of the 12 week double blind 31.6 (SD 4.7) with a reduction to 22.1 (SD 12.2) at the end of the 12 week double blind phase. The primary endpoint of change in IRLS Study Group severity rating scale sum score (an internationally accepted scoring system) at 12 weeks was significantly greater for oxycodone/naloxone prolonged release (–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), according to the pre-defined statistical analysis. The EPAR notes that using the ANCOVA Last Observation Carried Forward (LOCF) statistical analysis (comparable to the methods used for dopaminergic agents) the difference at 12 weeks was 7.2 units (p<0.001). The reduction on the IRLS Study Group severity rating scale translates into an improvement from “very severe” at the start of treatment to on average “moderate” or “mild” symptoms at the end of the double-blind phase. The minimum change in scale score that translates to clinically significant improvement in patients has been suggested as a difference at endpoint of 6 points or more on the IRLS scale and therefore the 16.6 change translates to a clinically meaningful reduction in the IRLS score.[12]

Key secondary endpoints were improvement of RLS in the Clinical Global Impression (CGI) severity scale; RLS-6 scores, (which measured symptom severity at different times of the day and night - data not included in the paper), quality of life (QoL-RLS-Scale) and change in pain using the numeric rating scale (NRS) for RLS pain, measured at baseline and then the end of the study period. Details of these along with responder rates are listed in the table in Appendix 1. All showed statistically significant improvement in favour of oxycodone/naloxone prolonged release tablets compared to placebo. 42% patients given oxycodone/naloxone prolonged release tablets during the double-blind phase were classified as remitters (with an IRLS Study Group severity rating scale sum score of 0 during treatment (symptom-free) or 10 or less at the end of maintenance), versus 19% for placebo ($p < 0.001$). Patients who had at least a 50% improvement in IRLS Study Group severity rating scale sum score at the end of the 12 week study were classified as responders which was found to be 57% oxycodone/naloxone prolonged release treated patients versus 31% of placebo treated patients. This corresponded with a CGI-2 change of condition of “much improved” or very much improved” for 67% of oxycodone/naloxone treated patients in comparison to 35% of patients given placebo ($p < 0.0001$).

A total of 30 patients from the enrolled population of 306 were excluded from the analysis of results. A supplementary appendix to the original paper reports that 12 subjects (3·9%) failed to satisfy major entry criteria or fulfilled exclusion criteria but entered the double-blind phase by the investigators by mistake; 11 (3·6%) subjects were excluded as they did not have a primary efficacy outcome measure after at least one week of treatment, as specified in the study protocol; 7 (2.3%) subjects were excluded due to serious noncompliance with the study procedures, because of obvious potential bias in the observation values. The medical monitors agreed to these exclusions during the blinded data review meeting.

20/150 (13%) patients discontinued oxycodone/naloxone prolonged release treatment in the double-blind phase because of tolerability problems. This compared to 10/154 (7%) in the placebo group. 10/150 (7%) patients in the oxycodone/naloxone prolonged release group and 30/154 (20%) patients in the placebo group withdrew because of lack of efficacy.

The open-label extension study was designed to investigate maintenance of treatment effect for up to a total of 52 weeks (40 weeks of treatment in the extension phase i.e. 52 weeks in total including the double-blind phase) in 197 patients. During this phase, patients were assessed at 4-weekly intervals. Inclusion criteria 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. Daily titration to the optimal dose was permitted up to a dose of oxycodone/naloxone 40/20 mg twice daily. 157/197 (80%) patients completed 40 weeks of treatment. Patients had a mean IRLS sum score of 15.4 (SD 11.2) at the start of the extension phase compared with 9.7 (SD 7.8) at week 40 (n=152; change 5.7). 9.7 corresponds to a mild symptom severity (0-10). These results showed a further slight improvement of the IRLS sum score compared to the results at the end of the double-blind phase (N.B. Mean IRLS sum score was 15.1 at the end of the 12 week phase for the oxycodone/naloxone treated patients). The treatment effect during the extension phase was independent of the treatment during the double-blind phase. 16/101 (15.8%) patients who had previously taken oxycodone/naloxone prolonged release discontinued treatment prematurely during the extension phase versus 24/96 (25%) patients who had previously taken placebo.

The main reasons were adverse events (AEs) (10/101 (9.9%) vs 11/96 (11.5%) and patient's choice (3/101 (2.9%) vs 8/96 (8.3%)). The discontinuation rate during the extension phase was approximately 20%, with 3% of this relating to lack of therapeutic effect. For comparison, discontinuation in the key RCT was more common in the placebo group than in the prolonged release oxycodone–naloxone group (57/154 [37%] vs 43/150 [29%]).[14] The mean daily dose of oxycodone/naloxone prolonged release tablets was almost identical and even slightly lower than the mean daily dose in the double-blind phase (18.12 mg vs 22.62 mg), with no difference in mean doses in the extension phase between the subgroups previously treated with either oxycodone/naloxone prolonged release tablets or placebo.[15] The secondary efficacy parameters including; reduction in the severity of illness, RLS-related pain and QoL, also showed further improvements when comparing the patients' condition at the end of the extension phase and at the end of the double-blind phase for those treated with oxycodone/naloxone prolonged release vs. placebo. (See table in Appendix 1). At the end of the extension phase, 43% of patients were classified as remitters, of which 22% had no symptoms.

Other efficacy data:

A meta-analysis evaluating pharmacological therapies for the treatment of RLS published in 2013, was identified.[16] 58 placebo-controlled and 4 active-comparator randomised controlled trials (RCTs) with 9569 patients were included, of which 12 trials were unpublished. The trials assessed the following drugs; cabergoline, lisuride, pergolide, pramipexole, ropinirole, rotigotine, sumanirole, levodopa, gabapentin, gabapentin encarbil, pregabalin, levetiracetam, topiramate, oxycodone, IV iron sucrose, IV iron dextran, ferrous sulphate and IV ferric carboxymaltose which were used for between 1 and 30 weeks. Only 1 of the 62 trials included in the meta-analysis assessed the use of oxycodone (without naloxone), which was compared to placebo and only included 11 patients. The paper states that the RCT found a high treatment efficacy for oxycodone, which confirms clinical experience with this preparation for use as monotherapy or add on treatment for RLS. However, it does conclude that due to there only being one trial published to date that they cannot draw final conclusions regarding the treatment of RLS with opioids. This meta-analysis was conducted before the publication of the RCT assessing prolonged release oxycodone and naloxone in RLS discussed above.

The randomised double-blind crossover-design placebo-controlled trial compared the use of oxycodone to placebo in 11 patients[17] and was included in the meta-analysis discussed above. Patients were tapered off all medication known to affect RLS prior to two baseline polysomnographic studies. Patients rated their symptoms for the two nights of the baseline studies (these were averaged in order to obtain the baseline score) and then were given either oxycodone 2.5 mg or placebo and the dose was gradually increased to therapeutic effect over approximately 2 weeks during which the patients also rated their symptoms; paraesthesia, motor restlessness & daytime alertness, on a daily basis, using a 0-4 scale (0=none, 1=mild, 2=moderate, 3=severe and 4=very severe symptoms). For the drug and placebo phase of the study, a combined rating of each symptom was obtained by adding daily ratings for the 2 weeks prior to the drug or placebo polysomnographic studies and ratings for the two nights of the appropriate polysomnographic studies. These values were then averaged. Titration was stopped at a maximum of 25 mg of oxycodone. Dosages were divided so that the patient was taking tablets 2 hours prior to bedtime, at bedtime and in the middle of the night, as required. Following this there was a further two nights of polysomnographic studies under double-blind conditions and a daily subjective rating of symptoms was also obtained. The capsules were then tapered to zero over 3 days. The second phase of the study was then carried out over a further 2 weeks using the same protocol as the first phase, with the patients being swapped over to the other treatment. At the end of the study patients were asked under double-blind conditions which capsule they preferred overall. 10/11 patients chose oxycodone, the 11th patient felt that although oxycodone gave her mild relief of RLS symptoms compared to placebo, it also caused mild daytime lethargy at the dosages used. On the self-rating scale, statistical improvement, on an average of 11.39 mg oxycodone, was demonstrated for; leg sensations (mean baseline score 2.65, mean placebo score 2.61, mean oxycodone treatment score 1.29 ($p < 0.009$)) and motor restlessness (mean baseline score 2.45, mean placebo score 2.58, mean oxycodone treatment score 1.21 ($p < 0.006$)) (please note the trial was not powered to show statistical significance); drowsiness the day after was also significantly improved whilst on oxycodone treatment compared to baseline or placebo treatment (mean baseline score 2.15, mean placebo score 1.79, mean oxycodone treatment score 1.11 ($p < 0.03$)). The polysomnographic studies showed that the number of periodic limb movements in sleep (PLMS)/hour of sleep was significantly reduced (mean baseline score 38.8, mean placebo score 52.9, mean drug score 18.4 ($p < 0.004$)). Sleep efficiency was significantly improved (mean baseline score 52.2, mean placebo score 45.7, mean drug score 70.4 ($p < 0.006$)) on an average of 15.9 mg oxycodone. There was no significant change in the number of awakenings/hours of sleep or in the percentage of slow wave sleep.

Summary of safety data:

During the double-blind phase of the RCT, 84% of patients in the oxycodone/naloxone prolonged release treated group reported any adverse event (AE) in comparison to 69% in the placebo group. The authors note that 73% if the active comparator group had AEs related to treatment whereas 43% of the patients in the placebo group reported AEs. The most frequently reported AEs for both the double-blind phase of the study and the extension phase were consistent with the safety profile of opioids and included; constipation (19% oxycodone/naloxone versus 5% placebo in the double-blind phase and 15% in the extension phase – 8% of the active comparator group were deemed to have clinically relevant constipation); nausea (17% oxycodone/naloxone versus 9% placebo in the double-blind phase with 10% in the extension phase); fatigue (29% oxycodone/naloxone versus 13% placebo with 10% in the extension phase); somnolence (11% oxycodone/naloxone versus 5% placebo with 8% in the extension phase) and hyperhidrosis (2% oxycodone/naloxone versus 2% placebo with 7% in the extension phase). During the double-blind and extension phases, 5/150 and 3/197 patients respectively in the oxycodone/naloxone group had serious treatment-related AEs, listed as; vomiting, constipation, ileus, subileus, acute flank pain, liver metastases, cholecystolithiasis, pleural effusion, peripheral arterial occlusive disease and duodenal ulcer (the latter five unlikely related to study drug). The incidence of augmentation was reported to be 0% - 63 patients reported worsening symptoms –1 of the patients in the active comparator group was deemed to be a potential case. This patient was reviewed by an expert who concluded it was not augmentation. For comparison, the frequency of augmentation during the first year of treatment with dopaminergic drugs is reported to be between 9 and 60%.[15,18] A lower number of patients in the active comparator group discontinued therapy in the double-blind phase of the study in comparison to the placebo group due to lack of therapeutic effect (7% oxycodone/naloxone treated patients versus 20% placebo treated patients). The dropout rates were comparable to those observed with first-line dopaminergic drugs used in less severely affected patients.[15] According to the EPAR, the discontinuation rate in the extension phase was approximately 20%, however only 3% of this was as a result of lack of therapeutic effect.

No case of abuse or misuse, tolerance or psychological dependence was reported during the double-blind or extension phase of the study. The EPAR states that as a result of a specific follow-up visit, 4 weeks after the end of the extension phase, 10/176 patients reported signs of physical dependence. 176/197 patients were reassessed for symptoms of physical and psychological dependence at a follow-up visit four weeks after the end of the open-label extension. Drug withdrawal symptoms occurred in one patient after 12 weeks of treatment and two patients after 1 year of treatment.[14]

The RCT of 11 patients reported that the only side-effects encountered were “minimal constipation” in two patients and “minimal daytime lethargy” at higher doses of oxycodone in one patient which decreased when the dosage was reduced. There were no dropouts from the study.[17]

Strengths and limitations of the evidence:

Strengths

- The validity of the RCT is likely to be high and risk of bias low due to the following reasons: Patient-Orientated Outcome, double-blinding, allocation concealment, adequate power/size, intention-to-treat analysis and follow-up.
- The inclusion criteria for the patients in the RCT reflect the licensed indication and potential population for whom oxycodone/naloxone prolonged release tablets may be an option.
- The primary outcome of change in IRLS Study Group severity rating scale sum score was significantly greater for 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). The minimum change in scale score that translates to clinically significant improvement in patients has been suggested as a difference at endpoint of 6 points or more on the IRLS scale.[12]
- The EMA notes that even when using a very conservative statistical approach, the magnitude of effect (decrease in mean IRLS of 5.9 points compared to placebo) was in line with or even slightly better than the results found in the placebo-controlled studies with dopamine agonists approved as first line treatments.

Limitations

- No published RCTs comparing oxycodone/naloxone prolonged release with an active comparator were found.
- Only one of the 62 trials included in the meta-analysis related to oxycodone and did not include any trials comparing the combination of oxycodone and naloxone.
- The oxycodone trial included in the meta-analysis only consisted of 11 patients and enrolled with idiopathic RLS who were given divided night-time doses of oxycodone or placebo over the course of two weeks.
- Intention to treat analysis and adequate follow-up occurred for the primary outcome only in the RCT.
- The extension phase of the RCT was open-label increasing the risk of bias. However different measures were put into place to minimise this risk such as placebo patients being able to enter the extension phase (comparable proportions from each arm entered); patients who had discontinued treatment due to loss of efficacy were permitted to enter, a week's down-titration prior to entering the extension to prevent carry over treatment effects; continued blinding about their double-blind treatment on entering the extension phase; comparable proportions of patients from both treatment arms joining the extension phase (101/150 oxycodone/naloxone prolonged release treated patients and 96/154 placebo patients).

Summary of evidence on cost effectiveness:

No published evidence on the cost-effectiveness of oxycodone/naloxone prolonged release tablets in the UK has been identified.

Prescribing and risk management issues:

- Oxycodone/naloxone is a Schedule 2 controlled drug (CD) and as such is subject to full CD requirements e.g. prescription requirements, safe custody, CD registers. Guidance (June 2006) issued by the Department of Health in England on prescribing and dispensing of Controlled Drugs requires in general, prescriptions for Controlled Drugs in Schedules 2 to be limited to a supply of up to 30 days' treatment; exceptionally, to cover a justifiable clinical need and after consideration of any risk, a prescription can be issued for a longer period, but the reasons for the decision should be recorded on the patient's notes[19]

- Concerns were raised by the Netherlands Medicines Evaluation Board that the use of oxycodone/naloxone could lead to tolerance and misuse. Therefore the Committee for Medicinal Products for Human Use (CHMP) were asked to carry out a review of the available data concerning the use of this product for RLS. Following analysis of the scientific data and discussion within the Committee, the CHMP agreed that the principle RCT[14] had convincingly shown that oxycodone/naloxone prolonged release is beneficial in the treatment of symptoms of severe to very severe RLS when standard therapy has failed. The CHMP concluded that the overall risk of tolerance and misuse was considered low and therefore the benefits of treatment outweigh the risks. The SPC advises that there is potential for development of psychological dependence (addiction) to opioid analgesics, including oxycodone/naloxone. It should be used with particular care in patients with a history of alcohol and drug abuse. Oxycodone alone has an abuse profile similar to other strong agonist opioids.[1]

- The Summary of Product Characteristics recommends treatment of patients with RLS with oxycodone/naloxone should be under the supervision of a clinician with experience in the management of RLS.[1]

- At least every three months during therapy with oxycodone/naloxone, patients should be clinically evaluated. Treatment should only be continued if it is considered effective and the benefit is considered to outweigh adverse effects and potential harms in individual patients. Prior to continuation of RLS treatment beyond 1 year, a discharge regimen by gradually tapering down of oxycodone/naloxone over a period of approximately one week should be considered to establish if continued treatment is indicated.[1]

- When a patient no longer requires opioid therapy, cessation of treatment by tapering down over a period of approximately one week is recommended in order to reduce the risk of a

withdrawal reaction.[1] Unused oxycodone/naloxone tablets must be returned by the patient to their pharmacy for disposal in order to reduce the risk of harm or abuse by others.

- Depending on the history of the patient, an overdose of oxycodone/naloxone may be manifested by symptoms that are either triggered by oxycodone (opioid receptor agonist) or by naloxone (opioid receptor antagonist). Symptoms of oxycodone overdose include miosis, respiratory depression, somnolence progressing to stupor, skeletal muscle flaccidity, bradycardia as well as hypotension. Coma, non-cardiogenic pulmonary oedema and circulatory failure may occur in more severe cases and may lead to a fatal outcome. Symptoms of a naloxone overdose alone are unlikely. Management of intoxication is outlined in the SPC and the patient information leaflet (PIL) advises to contact a doctor immediately if they experience any of the signs and symptoms of overdose.

- Caution is advised in treating restless legs syndrome patients with additional sleep apnoea syndrome with oxycodone/naloxon due to the additive risk of respiratory depression. No data about the risk exist because in the clinical trial patients with sleep apnoea syndrome were excluded.[1]

- The major risk of opioid excess is respiratory depression. Caution must be exercised when administering oxycodone/naloxone to elderly or infirm patients, patients with opioid-induced paralytic ileus, patients presenting severely impaired pulmonary function, patients with sleep apnoea, myxoedema, hypothyroidism, Addison's disease (adrenal cortical insufficiency), toxic psychosis, cholelithiasis, prostate hypertrophy, alcoholism, delirium tremens, pancreatitis, hypotension, hypertension, pre-existing cardiovascular diseases, head injury (due to the risk of increased intracranial pressure), epileptic disorder or predisposition to convulsions, or patients taking MAO inhibitors.[1]

- The SPC lists the following contraindications: hypersensitivity to the active substances or to any of the excipients; any situation where opioids are contraindicated; severe respiratory depression with hypoxia and/or hypercapnia; severe chronic obstructive pulmonary disease; cor pulmonale; severe bronchial asthma; non-opioid induced paralytic ileus; moderate to severe hepatic impairment; additionally for restless legs syndrome, history of opioid abuse.[1]

- A US observational study found that when used for chronic non-cancer pain, the use of long-acting preparations of opioids was associated with an approximately two-fold higher risk of unintentional overdose compared with using short-acting preparations of opioids. The study found the risk of unintentional overdose was greatest during the first 2 weeks of treatment and when higher daily doses of opioids were used.[20] Following completion of an evidence commentary of this study,[21] NICE summarised that a number of important limitations to the study prevent firm conclusions being made and that prescribers should continue to follow guidance in the Rapid Response Report on Reducing dosing errors with opioid medicines.[22] The key points from this report are: When opioid medicines are prescribed, dispensed or administered, in anything other than acute emergencies, the

healthcare practitioner concerned, or their clinical supervisor, should:

- Confirm any recent opioid dose, formulation, frequency of administration and any other analgesic medicines prescribed for the patient. This may be done for example through discussion with the patient or their representative (although not in the case of treatment for addiction), the prescriber or through medication records.
- Ensure where a dose increase is intended, that the calculated dose is safe for the patient (e.g. for oral morphine or oxycodone in adult patients, not **normally** more than 50% higher than the previous dose).
- Ensure they are familiar with the following characteristics of that medicine and formulation: usual starting dose, frequency of administration, standard dosing increments, symptoms of overdose, common side effects.

- Substances having a CNS-depressant effect (e.g. other opioids, sedatives, hypnotics, antidepressants, phenothiazines, neuroleptics, antihistamines and antiemetics) may enhance the CNS-depressant effect (e.g. respiratory depression) of oxycodone/naloxone prolonged release.[1] Prescribing of opioids for analgesia should therefore be avoided.
- Alcohol may enhance the pharmacodynamic effects of oxycodone/naloxone prolonged release; concomitant use should be avoided.

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Pramipexole tablets (Mirapexin brand licensed for RLS)	88 micrograms daily to max of 540 micrograms daily	88 microgram x 30 = £11.24 180 microgram x 30 = £22.49; 100 = £74.95.*	£137- £821
Ropinirole tablets	250 micrograms daily for 2 days then 500 micrograms daily for 7 days, increase to max of 4 mg daily	500 micrograms x 28 = £15.75; 2 mg x 28 = £31.51	£205- £821
Rotigotine patches	1 x 1 mg/24hrs patch applied daily to a maximum of 1 x 3 mg/24hrs patch applied daily	1 mg/24hrs, 28 = £77.24. 3 mg/24hrs, 28 = £102.35.	£1007- £1334
Oxycodone/naloxone prolonged release tablets	1 x 5 mg/2.5 mg tablet every 12 hours to a maximum of 60 mg/30 mg daily	5 mg/2.5 mg tab x 28 = £21.16. 10mg/5mg tab x 56 = £42.32. 20 mg/10 mg tab x 56 = £84.62.**	£552- £1655
Gabapentin	100 mg to 300 mg initially to a maximum of 2400 mg/day****	100 mg cap x 100 = £2.81. 400 mg cap x 100 = £4.33.	£10- £95

Pregabalin	25 mg daily initially up to a maximum of 300 mg daily****	25 mg cap x 56 = £64.40. 300 mg cap x 56 = £64.40.	£315

Costs based on MIMS list prices October 2015
This table does not imply therapeutic equivalence of drugs or doses.
* No 540 microgram strength exists, therefore 3 x 180 mcg would need to be prescribed if the patient were on the maximum dose
**No 30mg/10mg oxycodone MR tablet exists, therefore if a patient were to require the maximum dose of 60mg/30mg daily, the costs have been worked out by assuming 1 x 20mg/10mg tablet and 1 x 10mg/5mg tablet twice daily has been prescribed.
*** Dose recommended in RLS Foundation guidelines 2008[6]
**** Dose recommended by CKS

Associated additional costs or available discounts:

Constipation is classed as a common side-effect with oxycodone/naloxone prolonged release tablets and management of this AE may result in additional prescribing costs.

Productivity, service delivery, implementation:

This is an alternative preparation with no new service delivery necessary. If patients with RLS are residents at a nursing home then there may be an impact on nursing time with regards to two signatures being required for administration of a controlled drug.

Anticipated patient numbers and net budget impact:

RLS has a prevalence of 1.9% - 4.6% in Northern Europeans adults[4] and the number of adults in Lancashire is 78.6% of 1.5 million = 1,179,000 adults.

1.9% of 1,179,000 = 22,401 adults whereas 4.6% of 1,179,000 = 54,234 adults.

About 2-3% of patients have moderate to severe symptoms.[23]

2% of 22 401 – 54 234 = 448 - 1085 adults with moderate to severe symptoms of RLS in Lancashire. 3% of 22 401 – 54 234 = 672 – 1627 adults with moderate to severe symptoms of RLS in Lancashire.

If we assume 20% patients with RLS require drug treatment,[24] this equates to 90 - 325 adults across Lancashire.

Dopamine agonists have been reported as alleviating symptoms in at least 70% of patients.[25]

30% of 90 - 325 adults is equal to 27 - 98 adults potentially requiring treatment with oxycodone/naloxone prolonged release tablets for RLS. As Targinact® is only licensed for severe to very severe RLS, anticipated number of patients is likely to be at the lower end of this scale.

Using the mean daily dose of 21 mg daily from the double-blind phase of the key RCT, this would equate to 1 x 10mg oxycodone/naloxone prolonged release tablet 12 hourly at a cost of £42.32 for 56 tablets. This is equivalent to an annual cost of £550.16 per patient. Therefore potential annual cost for 27 patients is £14 854.

The manufacturer of oxycodone/naloxone prolonged release tablets were able to provide the following estimates of anticipated patient numbers and net budget impact:
Population in Lancashire is 1,165,000 and for the UK is 63,866,000 based on December 2014 estimates from the Office of National Statistics.

Following market research and discussions with UK RLS experts it is estimated that there are 53705 patients with RLS and 18.75% are treated with a second dopamine agonist or levodopa. Based on recommendations from UK experts the estimate for eligible patients in the UK is 1133. This is 2.1% of the total RLS population.

(One year after the launch of oxycodone/naloxone prolonged release tablets for RLS in Germany, the number of RLS patients treated is approximately 2.4% of the total number diagnosed with RLS (3914 of 350,357). This is in-line with the estimate for the UK of 2.1%.).

Estimate: 1,165,000 / 63,686,000 x 1133 eligible patients = 21 patients in Lancashire.

Using the mean daily dose from Trenkwalder et al study of 21mg for the double-blind phase and 18mg for the extension phase, this would equate to 1 x 10mg tablet 12 hourly; at a cost of £42.32 per pack of 56 tablets.

Assuming 13 x 56 tablet packs per annum this would be £550.16 per annum. Potential annual cost of 21 patients is £11 553.

Innovation, need, equity:

Oxycodone/naloxone prolonged release is not an innovative treatment in that opioid analgesics have been a potential off-label option for the treatment of RLS for many years. However it offers an additional licensed option if dopaminergic agents have failed in patients with moderate to severe RLS with the benefit of reduced constipation due to the naloxone portion of the preparation compared to the off label use of oxycodone.

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Appendix 1

Table: Summary of key oxycodone / naloxone RCT relevant to use in Restless Legs Syndrome

<table>
<tr><th>Ref</th><th>Trial design</th><th>Patients / Trial subjects</th><th>Trial intervention and comparison</th><th>Outcomes: Primary endpoint (mITT)</th><th>Outcomes: Key secondary / exploratory endpoints</th><th>Grading of evidence / risk of bias</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr>
<td>Trenkwalder C et al

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</td>
<td>12 week randomised placebo-controlled double-blind trial followed by 40 week open-label extension phase where all patients were prescribed oxycodone / naloxone

n= 306 (randomly assigned) n=276 included in the</td>
<td>
<table>
<tr><td></td><td>Prolonged release oxycodone–naloxone group</td><td>Placebo group</td></tr>
<tr><td>Double-blind safety population</td><td>n=150</td><td>n=154</td></tr>
<tr><td>Age (years)</td><td>63.1 (11.4)</td><td>61.7 (11.0)</td></tr>
<tr><td>Women</td><td>97 (65%)</td><td>105 (68%)</td></tr>
<tr><td>White ethnic origin</td><td>149 (99%)</td><td>154 (100%)</td></tr>
<tr><td>BMI (kg/m^2)</td><td>27.9 (4.3)</td><td>28.5 (5.4)</td></tr>
<tr><td>Duration of symptoms (years)</td><td>10.2 (9.8)</td><td>10.4 (10.2)</td></tr>
<tr><td>Duration of previous treatment (years)</td><td>4.8 (4.0)*</td><td>5.2 (4.4)</td></tr>
<tr><td>Full</td><td>n=132</td><td>n=144</td></tr>
</table>
</td>
<td>Patients were randomly assigned to: placebo (n=154) or oxycodone 5 mg / naloxone 2.5 mg prolonged release tablets (n=150) twice daily which could be up titrated in the first 6 weeks to a maximum of oxycodone 40 mg / naloxone 20</td>
<td>For the double-blind phase; change from baseline to 12 weeks in international RLS Study Group severity rating scale sum score. (Scores range from 0 (no symptoms) to 40 (very severe symptoms)).

Mean International RLS Study Group severity rating scale sum score at baseline (after washout) was 31·7 (SD 4·4) for oxycodone/naloxone group and 31.6</td>
<td>Key Secondary endpoints :

Change in clinical global impression score (CGI-1) severity of disease :
Oxycodone/naloxone:
Baseline score 5.24 (0.88)
End of study 2.99 (1.48) (p<0.0001)
Placebo:
Baseline score 5.29 (0.85)
End of study 4.10 (1.71) (p<0.0001)
Extension phase
baseline score 3.15 (1.62)
End of extension phase 2.45 (1.23)
Change of severity of RLS during the day at rest (RLS-6 rating scale):
Oxycodone/naloxone:
Baseline score 6.70</td>
<td>Patient-oriented outcome measure?: Yes IRLS Study Group Severity rating

Allocation concealment?: Yes

Blinded if possible?: Double-blinded for first 12 weeks then open-label for 40 weeks

Intention to treat analysis?:?Ye</td>
</tr>
</table>

The Lancet Neurology 12:12;1141 -1150	primary analysis n=197 in open-label extension	analysis population			mg twice daily in weekly fixed, symmetrical increments — i.e. both 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 maintained for a further 6 weeks and then down-titrated within 1 week to	(SD 4.7) for the placebo group. Change in International RLS Study Group severity rating scale sum score at 12 weeks for prolonged release oxycodone–naloxone –16·6 vs. placebo –9·5 in the full analysis population (difference at 12 weeks 8·15 (95% CI 5·46–10·85 p<0·0001)).	(2.19) • End of study 2.50 (2.69) Placebo: • Baseline score 6.69 (2.51) • End of study 4.44 (3.30) (p<0.0001) Extension phase • Baseline score 2.77 (2.88). • End of extension phase 1.36 (1.69) Restless legs syndrome leg or arm pain score NRS pain score (numerical 11-point rating scale from 0–10 where 0 is pain is not present and 10 is severe, disabling pain): Oxycodone/naloxone: • Baseline score 6.57 (SD 2.53) • End of study 2.65 (SD 2.61) Placebo: • Baseline score 6.54 (SD 2.78) • End of study 4.63 (SD 3.21) (p<0.0001) Extension phase: • Baseline score 3.02 (2.84) • End of extension phase 1.58 (1.82)	s did not include 30 of the randomly allocated patients in the primary analysis, however full analysis set seems to have been used to calculate results. Adequate power/size?: Yes, power calculations detailed in trial protocol Adequate follow-up (>80%)?: Double-blind safety population n = 304 whereas full analysis population n= 276 and per
		RLS diagnostic index sum score	16.5 (1.9)	16.5 (2.0)				
		International RLS Study Group severity rating scale sum score	28.6 (5.4)	27.6 (5.5)				
		Previous treatment for restless legs syndrome†						
		Dopamine agonists	48 (36%)	43 (30%)				
		Dopamine agonists and other treatments	22 (17%)	29 (20%)				
		Levodopa	28 (21%)	44 (31%)				
		Levodopa and other treatments except dopamine agonists	4 (3%)	3 (2%)				
		Data are mean (SD) or n (%) *Data missing for one patient †For patients receiving ongoing						

		dopaminergic treatment at screening (n=221) **Inclusion criteria:** • 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 • symptoms for ≥6 months • International RLS Study Group severity rating scale sum score of ≥15 at screening (indicative of at least moderate severity) • daytime onset of symptoms before 1800 h ≥4 days per week • failed treatment of symptoms - 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 • no regular intake of opioid-containing drugs at any time before enrolment **Exclusion criteria:** • Secondary RLS • RLS associated with previous	oxycodone 5·0 mg, naloxone 2·5 mg, twice per day, which was also the starting dose for open-label treatment phase. Efficacy and safety assessed weekly for 4 weeks and at weeks' 8 and 12. During the 40-week extension phase, patients were assessed at 4-weekly intervals. Titration to the best dose was		Proportion of treatment responders at the end of the 12 week study: At least 50% improvement in sum score International RLS Study Group severity rating scale: • Oxycodone/naloxone 75/132 (57%) • Placebo 45/144 (31%) (p<0.0001) Clinical global impression-2 (CGI-2) change of condition ("much improved" or "very much improved"): • Oxycodone/naloxone 88/132 (67%) • Placebo 50/144 (35%) (p<0.0001) International RLS Study Group severity rating scale remitters (sum score of 0 during treatment (symptom-free) or 10 or less at the end of maintenance): 12 week study: • Oxycodone/naloxone 55/132 (42%) • Placebo 28/144 (19%) (p<0.0001) End of extension phase: • Oxycodone/naloxone	protocol population n = 174 Full analysis set used for primary outcome (follow-up ~90%) Level 1 or 2 evidence based on POO, double-blinding, allocation concealment, adequate power/size and follow-up. Risk of bias: low based on POO, double-blinding, allocation concealment, adequate power/size and follow-up.

		or concomitant use of dopamine-receptor blocking drugs • h/o or current sleep apnoea syndrome, narcolepsy, myoclonus epilepsy, hallucinations or psychotic episodes • h/o acute clinical augmentation according to Max Planck Institute diagnostic criteria • treatment with naloxone or naltrexone within 30 days of study entry • C/I or hypersensitivity to oxycodone, naloxone, related products or other ingredients • Patients with clinically evident respiratory disorders, clinically relevant constipation or ileus • concomitant or prior medication likely to have influenced sleep architecture or motor manifestations during sleep or other central nervous system (CNS) depressants were not permitted. • Current alcohol or drug misuse, h/o opioid misuse • Taking an investigational	permitted daily up to oxycodone 40 mg, naloxone 20 mg, twice per day.		85/197 (43%) were remitters, of which 43/197 (22%) had no symptoms Changes RLS quality of life summary question 12 score ("To what degree did your RLS symptoms impair your quality of life during the last 4 weeks?", from 1 (not at all) to 6 (extremely): Oxycodone/naloxone: • Baseline score 4.3 (0.93) • End of study 2.91 (1.48) Placebo: • Baseline score 4.27 (1.10) • End of study 3.64 (1.67) (p<0.0001) Extension phase • Baseline score 2.89 (1.55) • End of extension phase 2.08 (1.07) Incidence of augmentation reported to be 0% - 63 patients reported worsening symptoms – only 1 patient in the active comparator group	

		drug within 30 days before study entry • Serum ferritin < 30 µg/L at screening • Taking monoamine oxidase inhibitors within 2 weeks before screening • Shiftworkers Note stable non-opioid analgesic regimens for reasons other than RLS could be continued during the study Inclusion criteria for the 40 week extension 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.			was deemed to be a potential case - reviewed by an expert who concluded it was not augmentation. Change in mean International RLS Study Group severity rating scale sum score at 12 weeks: • oxycodone/naloxone (-16・6) • placebo (-9・5) in the full analysis population • difference at 12 weeks; 8.15 (95% CI 5.46-10.85); (p<0・0001). Any AE: • Oxycodone/naloxone 126/150 (84%) • Placebo 106/154 (69%) • End of extension phase 150/197 (76%) Any adverse event causing withdrawal from study: • Oxycodone/naloxone 22/150 (15%) • Placebo 10/154 (7%) • End of extension phase 18/197 (9%)	

					Any severe AE related to treatment: • Oxycodone/naloxone 17/150 (11%) • Placebo 7/154 (5%) • End of extension phase 18/197 (9%) Any serious AE related to treatment: • Oxycodone/naloxone 5/150 (3%) • Placebo 0/154 (0%) • End of extension phase 3/197 (2%) Mean changes at weeks 2, 3, 4, and 8 and based on a post-hoc analysis of the safety population (7·03, 95% CI 4·36–9·70; p<0·0001). Mean sum score of 15·4 throughout the extension phase (11·2) at the start compared with 9·7 (SD 7·8) at week 40(n=152; change 5·7).	
Footnotes						

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

Appendix 2 Restless Legs Syndrome Rating Scale accessed on 7/10/15 at http://www.medicine.ox.ac.uk/bandolier/booth/RLS/RLSratingscale.pdf

Restless Legs Syndrome Rating Scale

Have the patient rate his/her symptoms for the following ten questions.
The patient and not the examiner should make the ratings, but the examiner should be available to clarify any misunderstandings the patient may have about the questions.
The examiner should mark the patient's answers on the form.

In the past week.... (1) Overall, how would you rate the RLS discomfort in your legs or arms? _ (4) Very severe _ (3) Severe _ (2) Moderate _ (1) Mild _ (0) None	**In the past week....** (6) How severe was your RLS as a whole? _ (4) Very severe _ (3) Severe _ (2) Moderate _ (1) Mild _ (0) None
In the past week.... (2) Overall, how would you rate the need to move around because of your RLS symptoms? _ (4) Very severe _ (3) Severe _ (2) Moderate _ (1) Mild _ (0) None	**In the past week....** (7) How often did you get RLS symptoms? _ (4) Very often (6 to 7 days in 1 week) _ (3) Often (4 to 5 days in 1 week) _ (2) Sometimes (2 to 3 days in 1 week) _ (1) Occasionally (1 day in 1 week) _ (0) Never
In the past week.... (3) Overall, how much relief of your RLS arm or leg discomfort did you get from moving around? _ (4) No relief _ (3) Mild relief _ (2) Moderate relief _ (1) Either complete or almost complete relief _ (0) No RLS symptoms to be relieved	**In the past week....** (8) When you had RLS symptoms, how severe were they on average? _ (4) Very severe (8 hours or more per 24 hour) _ (3) Severe (3 to 8 hours per 24 hour) _ (2) Moderate (1 to 3 hours per 24 hour) _ (1) Mild (less than 1 hour per 24 hour) _ (0) None
In the past week.... (4) How severe was your sleep disturbance due to your RLS symptoms? _ (4) Very severe _ (3) Severe _ (2) Moderate _ (1) Mild _ (0) None	**In the past week....** (9) Overall, how severe was the impact of your RLS symptoms on your ability to carry out your daily affairs, for example carrying out a satisfactory family, home, social, school or work _ (4) Very severe _ (3) Severe _ (2) Moderate _ (1) Mild _ (0) None
In the past week.... (5) How severe was your tiredness or sleepiness during the day due to your RLS symptoms? _ (4) Very severe _ (3) Severe _ (2) Moderate _ (1) Mild _ (0) None	**In the past week....** (10) How severe was your mood disturbance due to your RLS symptoms - for example angry, depressed, sad, anxious or irritable? _ (4) Very severe _ (3) Severe _ (2) Moderate _ (1) Mild _ (0) None
Sum of scores =	
Scoring criteria are: Mild (score 1-10); Moderate (score 11-20); Severe (score 21-30); Very severe (score 31-40)	
1. Answers for this IRLS are scored from 4 for the first (top) answer (usually "very severe") to 0 for the last answer (usually none). All items are scored. The sum of the item scores serves as the scale score. The International Restless Legs Syndrome Study Group holds the copyright for this scale.	

Appendix 3

Evidence classification scheme developed by the International Restless Legs Syndrome Study Group for evaluating long-term studies of therapeutic interventions for restless legs syndrome/Willis–Ekbom disease.

Class	Description
I	An adequately powered prospective, randomized, controlled, clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following 5 criteria must be met: _ Randomization is concealed _ Primary outcomes are clearly defined _ Exclusion and inclusion criteria are clearly defined _ Dropouts and crossovers are adequately accounted for, with numbers sufficiently low to have minimal potential for bias _ Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences
II	Prospective, matched-group, cohort study in a representative population with masked outcome assessment that meets all of the requirements for a Class I study or a randomized controlled trial in a representative population except that it lacks one of the five criteria for a Class I study.
III	Any of the following study designs qualify a_{IRLSSG}. A controlled trial that includes well-defined natural history control subjects or patients serving as their own controls in a representative population in which outcome assessment is independent of patient treatment b_{IRLSSG}. A large prospective case series or prospective open-label clinical trial in a representative population, in which outcome assessment is well-defined and is independent of patient treatment c_{IRLSSG}. A large retrospective case series or retrospective evaluation of data from a clinical trial in a representative population, in which outcome assessment is well-defined and is independent of patient treatment IV An uncontrolled study, case series, case reports, or expert opinion

Adapted from Agency for Healthcare Research and Quality and European Federation of Neurological Societies.
Rating of recommendations for therapeutic interventions.

Rating	Requires at least	Intervention is
A	One convincing Class I study or at least two consistent, convincing, Class II studies	Effective, ineffective, or harmful

B	One convincing Class II study or overwhelming[a] Class IIIIRLSSG evidence	Probably effective, probably ineffective, or probably harmful
c	Two convincing Class IIIIRLSSG studies	Possibly effective, possibly ineffective, or possibly harmful
Good practice points	Consensus of expert opinion	

[a] Overwhelming was interpreted for long-term studies to mean either one large well-defined prospective study of a long duration (3 or more y) with clear outcome results or several class III studies with almost all having the same result.

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