CNS Drugs (2015) 29:511–518
DOI 10.1007/s40263-015-0254-y

ADIS DRUG EVALUATION

Oxycodone/Naloxone PR: A Review in Severe Refractory Restless Legs Syndrome

James E. Frampton[1]

Published online: 2 July 2015
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Abstract An oral, fixed-dose combination of prolonged-release (PR) oxycodone with PR naloxone (Targin®, Targiniq®, Targinact®; hereafter referred to as oxycodone/naloxone PR) is approved in Europe for the second-line symptomatic treatment of patients with severe to very severe idiopathic restless legs syndrome (RLS), after failure of dopaminergic therapy. Coadministration of naloxone represents a targeted approach to counteracting opioid-induced bowel dysfunction without compromising therapeutic efficacy; because of its very low oral bioavailability, naloxone blocks the action of oxycodone at opioid receptors locally in the gut. The efficacy of oxycodone/naloxone PR in patients with severe RLS inadequately controlled by previous (mainly dopaminergic) treatment has been demonstrated in RELOXYN, a 12-week, randomized, double-blind study with a 40-week open-label extension. In this pivotal study, oxycodone/naloxone PR significantly improved RLS symptoms compared with placebo from week 2 onwards; a beneficial effect of oxycodone/naloxone PR was maintained through 1 year of treatment. Furthermore, improvements in RLS symptoms in oxycodone/naloxone PR recipients were accompanied by similarly sustained improvements in disease-specific quality of life and subjective sleep variables. Oxycodone/naloxone PR was generally well tolerated, with a treatment-related adverse event profile (e.g. gastrointestinal disorders, CNS disorders, fatigue and pruritus) that was consistent with that expected for opioid therapy. Notably, there were no confirmed cases of augmentation among oxycodone/naloxone PR recipients throughout the course of the study. Results from the well-designed RELOXYN trial have thus demonstrated the value of oxycodone/naloxone PR as a second-line therapy for severe refractory RLS; further investigation of this combination product as a first-line treatment for severe RLS is now warranted.

Oxycodone/naloxone PR in severe refractory RLS: a summary
Oral PR formulation combining oxycodone (opioid receptor agonist) and naloxone (opioid receptor antagonist) in a 2:1 ratio
Naloxone has very low oral bioavailability and is coadministered to counteract opioid-induced bowel dysfunction
Associated with improvements in RLS symptoms that are clinically and statistically significant in the short-term and maintained over the long-term
Also associated with sustained improvements in disease-related quality of life and sleep parameters
Tolerability consistent with that established for oxycodone in the treatment of severe pain
Not associated with RLS augmentation

The manuscript was reviewed by: ***A.E. Cavanna***, Department of Neuropsychiatry, BSMHFT and University of Birmingham, Birmingham, UK; ***S. di Biase***, Neurology Unit, Department of Experimental and Clinical Medical Sciences, University of Udine Medical School, Udine, Italy; ***L. Ferini-Strambi***, Department of Neurology, Universita Vita-Salute San Raffaele, Milan, Italy; ***Y. Inoue***, Department of Somnology, Tokyo Medical University, Tokyo, Japan.

✉ James E. Frampton
demail@springer.com

[1] Springer, Private Bag 65901, Mairangi Bay 0754, Auckland, New Zealand

1 Introduction

Restless legs syndrome (RLS), also known as Willis-Ekbom disease, is a common, sensorimotor neurological disorder characterized by the following clinical criteria, all of which must be present in order to confirm the diagnosis: (1) an urge to move the legs usually accompanied or caused by uncomfortable sensations in the legs; (2) symptoms begin or worsen during periods of rest or inactivity; (3) symptoms only occur or are worse in the evening and night than during the day; (4) symptoms are partially or fully improved by movement; and (5) symptoms cannot be solely accounted for by another medical or behavioural condition [1]. It primarily results in sleep disruption and subsequent daytime functional impairment, particularly for individuals with moderate to severe symptoms; consequently, the negative effects of RLS on patients' health-related quality of life (QOL) can be substantial, as can the economic burden to the patient and their family and to society as a whole (e.g. in terms of lost productivity) [2, 3].

RLS affects ≈5–15 % of adults across Northern, Western and Southern European countries, and is sufficiently severe to require medical intervention in 2.5 % of cases [4]. RLS prevalence is higher in women than in men, and increases with increasing age [5]. While the main underlying pathophysiological mechanism of RLS is generally thought to be dysfunctional dopaminergic modulation of neuronal excitability, additional abnormalities in other central neurotransmitters systems (e.g. iron, GABAergic and opioid) have been identified and their interaction with the dopaminergic system could be an essential step for symptom expression [6–8].

Dopaminergic agents, in particular nonergot dopamine agonists (NEDAs), such as pramipexole, ropinirole and rotigotine, have traditionally been the drugs of choice for adults with moderate to severe RLS, and are licenced for this indication in Europe [8–11]. The first such agent shown to be successful in the treatment of RLS was levodopa [12]; this dopamine precursor is still used occasionally in some European countries, namely Germany, Austria and Switzerland, mainly for the on-demand treatment of intermittent (as opposed to daily) RLS symptoms [9]. Although initially effective, the usefulness of dopaminergic agents may be limited by subsequent loss of efficacy (tolerance) and adverse events, including daytime sleepiness, impulse control disorders and the development of augmentation [13]. The latter, which is characterized by an overall worsening in RLS symptom severity compared with the pretreatment level, represents the most important long-term complication of dopaminergic treatment [9, 12]. Although augmentation is most common during long-term treatment with levodopa (up to 60 % of patients), it is still a frequent occurrence during long-term treatment with NEDAs (up to 40 % of patients) [10, 12].

International [13] and European [14] guidelines now also recommend pregabalin, gabapentin enacarbil and gabapentin as alternatives to dopaminergic agents for the first-line treatment of RLS; these α2δ calcium channel ligands may be preferred in patients presenting with, for example, severe sleep disturbance (disproportionate to other RLS symptoms), comorbid insomnia or generalized anxiety disorder, and RLS-related or comorbid pain [13]. Pregabalin appears to have a low(er) risk of augmentation relative to dopaminergic agents [15]; however, like gabapentin enacarbil and gabapentin, it is associated with sleepiness and dizziness [9, 12]. Moreover, the use of α2δ ligands is 'off-label', as they have yet to be approved for the treatment of RLS in Europe [8].

Similar to dopaminergic agents and α2δ ligands, opioids have also been shown to improve RLS symptoms; notwithstanding a historical paucity of clinical evidence, they are recognized to be of value in the treatment of patients with severe disease who are refractory to other drugs [16, 17]. Recently, an oral, fixed-dose combination of prolonged-release (PR) oxycodone with PR naloxone (Targin®, Targiniq®, Targinact®)—hereafter referred to as oxycodone/naloxone PR—has become the first opioid to be approved for the treatment of severe refractory RLS in many European countries [18]. Briefly, oxycodone/naloxone PR contains a 2:1 ratio of oxycodone, an opioid receptor agonist and naloxone PR, an opioid receptor antagonist [19]. Opioid agonists are very effective analgesics, although their long-term use is frequently complicated by adverse events, in particular the opioid-induced bowel dysfunction (constipation) that arises from undesired actions at opioid receptors in the gastrointestinal tract. Coadministration of oral oxycodone and naloxone represents a novel targeted approach to counteracting opioid-induced bowel dysfunction without compromising therapeutic efficacy. Because of its very low oral bioavailability, naloxone effectively blocks the undesired activity of oxycodone at opioid receptors in the gut, but not the desired (e.g. analgesic) activity of oxycodone at opioid receptors within the CNS [20–22].

This article reviews the pharmacological, therapeutic efficacy and tolerability data relevant to the use of oxycodone/naloxone PR in patients with severe refractory RLS [23].

2 Pharmacological Properties of Oxycodone/Naloxone

The pharmacological properties of oxycodone and naloxone administered individually and as oxycodone/naloxone PR have been reviewed previously [22]; only a brief overview is presented here.

Oxycodone is a semi-synthetic, full opioid receptor agonist that acts at μ-, κ- and δ-opioid receptors in the CNS and peripheral organs (e.g. intestine) [22]. It is a strong opioid analgesic with no ceiling effect, albeit the precise mechanism underlying the antinociceptive effect is unknown. Other (non-analgesic) pharmacological actions of oxycodone include effects on the CNS (e.g. respiratory depression), the gastrointestinal tract and other smooth muscle (e.g. constipation), and the cardiovascular system (e.g. orthostatic hypotension).

By contast, naloxone is a semi-synthetic, pure opioid antagonist that acts competitively at μ-, κ- and δ-opioid receptors in the CNS and peripheral organs (e.g. intestine) [22]. It has a very high affinity for opioid receptors and displaces, for example, opioid agonists. Naloxone exhibits no clinically relevant pharmacodynamic activity in the absence of any opioid agonism by other drugs.

Table 1 summarizes the key pharmacokinetic properties of oxycodone and naloxone. Studies involving the combination product have confirmed that the pharmacokinetic characteristics of oxycodone from oxycodone/naloxone PR are equivalent to those of oxycodone PR coadministered with naloxone PR [23]. They have also shown that plasma concentrations of oxycodone and, to a greater extent, naloxone are elevated in elderly subjects, as well as in patients with renal or hepatic insufficiency, particularly those with moderate or severe impairment. Oxycodone/naloxone PR should be administered with caution in elderly patients and patients with renal impairment or mild hepatic impairment; it is contraindicated in patients with moderate or severe hepatic impairment [23].

Although no formal drug-drug interaction studies have been conducted, oxycodone/naloxone PR is not expected to cause clinical drug-drug interactions with other co-administered drugs metabolized by the following cytochrome P450 (CYP) isoforms: 1A2, 2A6, 2C9/19, 2D6, 2E1 and 3A4 [22]. As oxycodone is primarily metabolised via the hepatic CYP3A4 system (Table 1), concurrently administered CYP3A4 inhibitors and inducers may lead to, respectively, an increase and decrease in plasma concentrations of oxycodone. A reduction in the dosage of oxycodone/naloxone PR may be required in patients being coadministered CYP3A4 inhibitors; caution is advised in patients being coadministered CYP3A4 inducers [23]. In comparison, oxycodone is only partially metabolised via the hepatic CYP2D6 pathway (Table 1); concomitant administration of CYP2D6 inhibitors did not have a clinically relevant effect on the elimination (or pharmacodynamics effects) of oxycodone [23]. The CNS-depressant effect (e.g. respiratory depression) of oxycodone may be enhanced by other CNS depressants; concomitant use of oxycodone/naloxone PR and alcohol should also be avoided [23].

3 Therapeutic Efficacy of Oxycodone/Naloxone PR

The efficacy of oxycodone/naloxone PR in patients with severe RLS inadequately controlled by previous treatment was evaluated in RELOXYN, a 12-week, randomized, double-blind, placebo-controlled study with a subsequent 40-week open-label extension that was conducted at 55 centres across Austria, Germany, Spain and Sweden [24].

Eligible patients were aged ≥18 years and had a diagnosis of primary (idiopathic) RLS according to essential and supportive diagnostic criteria (i.e. RLS diagnostic index sum score ≥11) [24]. They were required to have an International RLS Study Group (IRLSSG) severity rate scale sum score ≥15 (on a 0–40 scale, where scores of 1–10, 11–20, 21–30 and 31–40 indicate mild, moderate, severe and very severe symptoms, respectively). Patients were also required to have had symptoms for ≥6 months and to have failed previous (mainly dopaminergic)

Table 1 Key pharmacokinetic properties of oxycodone and naloxone [22, 23]

Oxycodone	Naloxone
High oral bioavailability (≤87 %)	Very low oral bioavailability (<3 %) due to high first-pass effect
Widely distributed (V_d: 2.5 L/kg) and ≈45 % bound to plasma protein	
Undergoes extensive hepatic metabolism (primarily via CYP3A4 and partly via CYP2D6); circulating metabolites include NM, OM and NC[a]	Undergoes extensive hepatic metabolism; principal metabolites include inactive naloxone-3-glucuronide
Excreted, along with its metabolites, in the urine (≤19 %) and faeces	Primarily excreted in urine
Mean plasma elimination half-life: ≈3 h	Mean plasma elimination half-life: ≈1 h after parenteral administration
Exposure increases with increasing hepatic impairment	Exposure increases with increasing hepatic impairment
Exposure increases with increasing renal impairment	Exposure increases with increasing renal impairment

CYP cytochrome P450, *NC* noroxycodone, *NM* noroxymorphone, *OM* oxymorphone, V_d apparent volume of distribution

[a] These metabolites, although active, do not contribute significantly to the overall pharmacodynamic (e.g. analgesic) effect of oxycodone

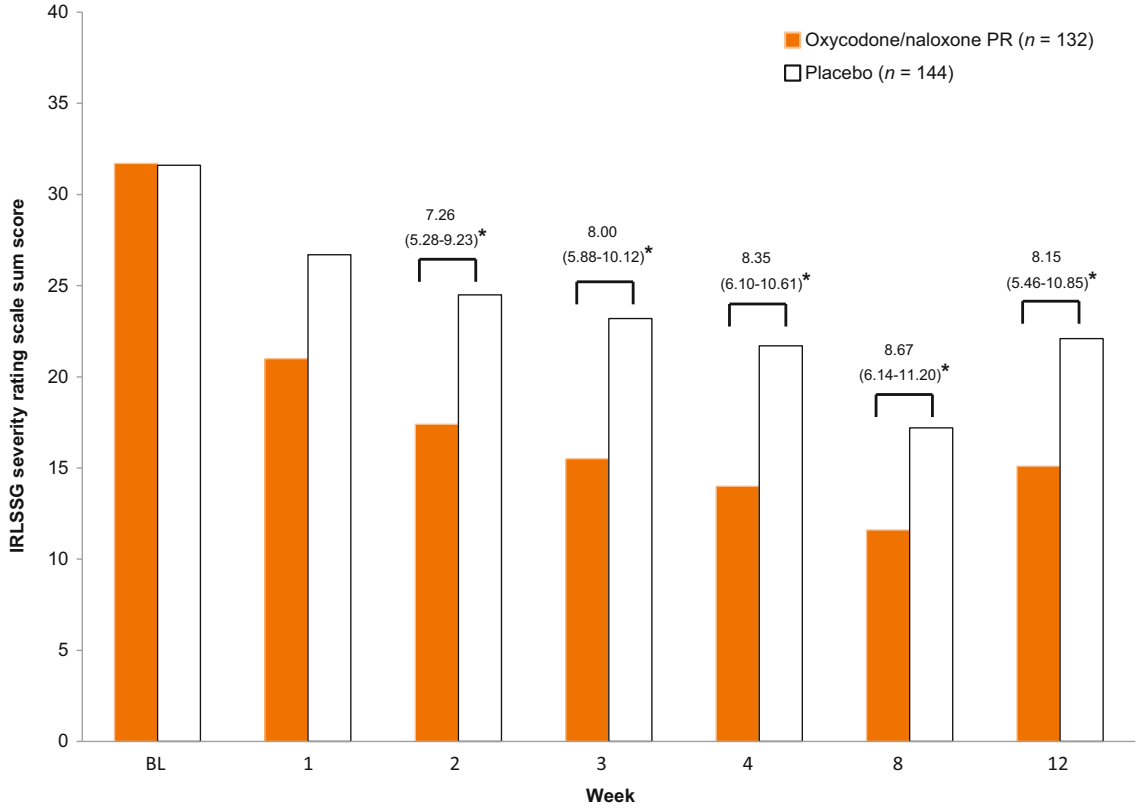

Fig. 1 International Restless Legs Syndrome Study Group (IRLSSG) severity rating scale sum scores [range: 0 (no symptoms) to 40 (very severe symptoms)] during the double-blind phase of the pivotal RELOXYN study [24]. The estimated treatment difference (95 % CI) is shown *above the bars*. *$p < 0.0001$ vs. placebo. *PR* prolonged release

treatment, either due to intolerable adverse events or inadequate efficacy.

The double-blind safety population comprised all but two of 306 randomly assigned patients who received oxycodone/naloxone PR 5/2.5 mg twice daily ($n = 154$) or placebo ($n = 150$) following a 1-week washout period [24]. During the first 6 weeks of treatment, the dosage of oxycodone/naloxone PR could be up-titrated to a maximum of 40/20 mg twice daily at the discretion of the investigator. The optimal dosage was administered for the remaining 6 weeks of the double-blind phase before being down-titrated within 1 week to 5/2.5 mg twice daily (also the starting dosage for the open-label treatment phase). Patients who completed the double-blind phase were eligible to enter the open-label extension, as were those who discontinued prematurely due to loss of efficacy after ≥8 weeks' treatment. As in the double-blind phase, the dosage of oxycodone/naloxone PR could be up-titrated to a maximum of 40/20 mg twice daily at the discretion of the investigator.

Efficacy analyses were performed on the full analysis population (all randomized patients who received at least one dose of study medication during the double-blinded phase and who had ≥1 week of double-blind assessment for the primary endpoint; $n = 132$ and 144 for oxycodone/naloxone PR and placebo) and used the mixed-effect model repeated measures approach (for the primary endpoint) or last observation carried forward method (for all secondary variables) [24].

Baseline characteristics of the double-blind safety and full analysis populations were well matched between the two treatment groups [24]. Based on the latter, oxycodone/naloxone PR recipients (of whom 65 % were women) had a mean age of 63.1 years, a mean duration of symptoms of 10.2 years, a mean duration of previous treatment of 4.8 years, a mean RLS diagnostic index sum score of 16.5 and a mean IRLSSG severity rating scale sum score of 28.6 at screening. Previous treatment for RLS included dopamine agonists alone or with other treatments (53 % of patients) and levodopa alone or with other treatments, excluding dopamine agonists (24 %).

Oxycodone/naloxone PR (mean dosage 21.9/11.0 mg/day) was more effective than placebo for the short-term treatment of patients with severe RLS inadequately controlled by previous (mainly dopaminergic) treatment [24].

Regarding RLS symptoms, a significant ($p < 0.0001$) difference favouring oxycodone/naloxone PR over placebo in the mean IRLSSG severity rating scale sum score was apparent from week 2 onwards (Fig. 1); the mean change in the IRLSSG severity rating scale sum score at week 12 (primary endpoint) significantly favoured oxycodone/naloxone PR over placebo in prespecified analyses of the full analysis population [treatment difference 8.15 (95 % CI 5.46–10.85); Fig. 1] and the per-protocol population [treatment difference 6.35 (95 % CI 3.13–9.57)] [24], and a post hoc analysis of the double-blind safety population [treatment difference 7.03 (95 % CI 4.36–9.70)] [24].

Furthermore, at the end of the double-blind phase, significantly ($p < 0.0001$) more oxycodone/naloxone PR than placebo recipients were classified as IRLSSG severity rating scale responders (57 vs. 31 %) or remitters (42 vs. 19 %) [24]. A responder was defined by a ≥50 % improvement in sum score; a remitter defined by a sum score of 0 during treatment (symptom-free) or ≤10 (mild symptoms) at the end of maintenance [24].

Similarly, significantly more oxycodone/naloxone PR than placebo recipients were Clinical Global Impression (CGI) change of condition item responders (67 vs. 35 %; $p < 0.0001$) [24]; additionally, both CGI severity of disease and therapeutic effect item scores at week 12 significantly favoured oxycodone/naloxone PR over placebo (Table 2).

Oxycodone/naloxone PR demonstrated greater efficacy than placebo on most secondary endpoints assessing disease-specific QOL, subjective sleep variables and RLS leg or arm pain (Table 2). In terms of disease-specific QOL, a positive effect of treatment with oxycodone/naloxone PR was seen across all five dimensions of burdens from RLS, including effects of RLS symptoms, effects of disturbed sleep, efforts to handle RLS symptoms, effect of pain caused by RLS and overall QOL; the QOL-RLS scale total score significantly ($p \leq 0.003$) favoured oxycodone/naloxone PR over placebo (abstract presentation) [25]. Median scores reflected moderate QOL impairment from RLS symptoms at baseline, with little impairment remaining at weeks 4 and 12 in oxycodone/naloxone PR recipients [25]. In terms of sleep, oxycodone/naloxone PR was associated with large, clinically relevant and statistically significant ($p < 0.001$) improvements compared with placebo in all Medical Outcomes Study sleep scale domains ('sleep quantity', 'optimal sleep', 'sleep disturbance', 'sleep adequacy', and 'sleep problems' indices I and II) and all four sleep-related questions of the RLS 6-item questionnaire ('sleep satisfaction', 'RLS symptom severity at falling asleep/during the night' and 'daytime tiredness') [abstract presentation] [26].

The beneficial effects of oxycodone/naloxone PR (mean dosage 18.1/9.1 mg/day) were sustained during the open-label extension phase, which included 197 patients (of whom 157 completed 40 weeks of treatment) [24]. The

Table 2 Results for secondary outcomes during the double-blind and extension phases of the pivotal RELOXYN trial [24]

Endpoint	12-week DB phase				40-week OL phase	
	OXY/NAL PR ($n = 132$)		PL ($n = 144$)		OXY/NAL PR ($n = 197$)	
	BL	End	BL	End	BL[a]	End
CGI item 1 (severity of disease) score	5.24	2.99**	5.29	4.10	3.15	2.45
CGI item 3 (therapeutic effect) score	–	1.73**	–	2.75	1.87	1.36
RLS-6 'severity during daytime when at rest' score	6.70	2.50**	6.69	4.44	2.77	1.36
RLS-QoL summary question 12 score	4.30[b]	2.91**	4.27[b]	3.64	2.89	2.08
Medical outcomes study sleep subscale scores						
Sleep adequacy	4.80	3.29**	4.86	4.03	3.31	2.82
Sleep quantity	5.15	6.25**	4.97	5.36	6.06	6.58
Daytime somnolence						
Drowsy or sleepy during the day	3.05	3.70	3.08	3.49	3.84	4.15
Trouble staying awake during the day	3.89	4.46**	4.10	4.33	4.61	4.73
Naps during the day	4.27	4.34*	4.28	4.33	3.31	4.54
Numerical rating scale pain score	6.57	2.65**	6.54	4.63	3.02	1.58

BL baseline, *CGI* Clinical Global Impressions rating scale, *DB* double-blind, *OL* open-label, *OXY/NAL PR* oxycodone/naloxone prolonged-release, *PL* placebo, *QoL* quality of life, *RLS* restless legs syndrome, *RLS-6* RLS 6-item questionnaire

* $p = 0.048$, ** $p < 0.0001$ vs. PL

[a] At the end of the DB phase, before the 1-week down-titration phase

[b] At screening, before the 1-week washout period

mean IRLSSG severity rating scale sum score was 15.4 at baseline (i.e. the start of the 1-week down-titration phase) compared with 9.7 at week 40. Notably, nearly one-half (43 %) of patients were classified as IRLSSG severity rating scale remitters at the end of the extension phase; almost one-quarter (22 %) had no symptoms. CGI severity of disease and therapeutic effect item scores, as well as most secondary endpoints assessing disease-specific QOL, sleep parameters and pain were improved at the end of the extension phase; however, the differences from baseline were not tested statistically.

4 Tolerability of Oxycodone/Naloxone PR

The adverse event profile of oxycodone/naloxone PR in patients with RLS in the RELOXYN study was consistent with that expected for opioid therapy in general and that already established for this fixed-dose combination in the treatment of severe pain [19, 24].

During the double-blind phase, 73 % of oxycodone/naloxone PR recipients compared with 43 % of placebo recipients reported at least one treatment-related adverse event (TRAE); 57 % of oxycodone/naloxone PR recipients reported at least one TRAE during the open-label extension phase [24]. The majority of TRAEs were of mild to moderate intensity; severe TRAEs occurred in 11 and 5 % of oxycodone/naloxone PR and placebo recipients, respectively, during the double-blind phase, and 9 % of oxycodone/naloxone PR recipients during the extension phase. Common TRAEs in oxycodone/naloxone PR recipients (i.e. incidence ≥5 % during the double-blind and/or extension phase) and their incidences in the double-blind phase were as follows: constipation (19 vs. 5 % for placebo), nausea (17 vs. 9 %), somnolence (11 vs. 5 %), fatigue (29 vs. 13 %), headache (13 vs. 7 %), dizziness (9 vs. 3 %), dry mouth (8 vs. 2 %), pruritus (7 vs. 3 %) and hyperhidrosis (2 vs. 2 %). Their incidences in the extension phase were as follows: constipation, 15 %; nausea, 10 %; somnolence, 8 %; fatigue, 10 %; headache, 3 %; dizziness, 5 %; dry mouth, 2%; pruritus, 4 %; and hyperhidrosis, 7 % [24].

Serious TRAEs were reported by six oxycodone/naloxone PR recipients (three during the double-blind phase and three during the open-label extension phase), and consisted of constipation ($n = 2$), vomiting, ileus, subileus and acute flank pain. No placebo recipient reported a serious TRAE [24].

Twelve (8 %) oxycodone/naloxone PR-treated patients reported clinically relevant constipation as an adverse event during the double-blind phase [24]. Whether these events were considered treatment-related and/or categorized as severe or serious was not specified.

The treatment discontinuation rate due to adverse events in the oxycodone/naloxone PR group was 15 % during the double-blind phase (vs. 7 % in the placebo group) and 9 % during the open-label extension phase [24]. Just under one-half of the oxycodone/naloxone PR-treated patients who terminated treatment early due to adverse events during the double-blind phase did so on account of commonly occurring adverse events, such as CNS disorders (dizziness, somnolence and headache) and fatigue.

There were no expert-confirmed cases of augmentation among 63 patients who reported worsening symptoms during the course of the trial and were assessed for this phenomenon [24].

Two oxycodone/naloxone PR recipients had drug withdrawal symptoms as an adverse event during the extension phase [19, 24]. In addition, 10 (5.7 %) of 176 patients reported signs of physical dependence at a follow-up visit 4 weeks after the end of the extension phase that was specifically designed to assess symptoms of physical and psychological dependence. However, the RELOXYN study protocol did not stipulate dose-tapering at the end of the extension phase (Sect. 3); tapering had not been performed in the majority of these patients [19]. There were no reports of psychological dependence throughout the study, including at the specific follow-up visit [19].

Similarly, there were no reports of opioid abuse/misuse or tolerance during either the double-blind or extension phases of the trial [19].

5 Dosage and Administration of Oxycodone/Naloxone PR

In many European countries, oxycodone/naloxone PR is approved for the second-line symptomatic treatment of adults with severe to very severe idiopathic RLS, after failure of dopaminergic therapy [23]. It is indicated for patients suffering from RLS for ≥6 months; RLS symptoms should be present daily and during daytime (≥4 days/week). Previous treatment with at least one dopaminergic agent should have lasted, in general, 4 weeks.

The recommended starting dosage of oxycodone/naloxone PR is 5/2.5 mg administered twice daily, with or without food [23]. If a higher dosage is required, it is recommended that oxycodone/naloxone PR be uptitrated at weekly intervals to a maximum of 60/30 mg/day. RLS treatment should be reviewed at intervals of ≤3 months; if therapy is no longer required, oxycodone/naloxone PR should be gradually tapered-off over a period of ≈1 week (to reduce the risk of withdrawal symptoms) [23]. The necessity of continuing treatment beyond 1 year should be determined beforehand, also by tapering off oxycodone/naloxone PR over a period of ≈1 week.

Local prescribing information should be consulted for full details of contraindications, special warnings and precautions, and drug interactions relating to the use of oxycodone/naloxone PR.

6 Current Status of Oxycodone/Naloxone PR in Restless Legs Syndrome

By demonstrating that oxycodone/naloxone PR is effective in the treatment in patients with severe RLS inadequately controlled by previous (mainly dopaminergic) therapy, the well-designed RELOXYN study confirmed the value of this combination product as a second-line therapy in this setting.

In the short term, oxycodone/naloxone PR recipients experienced an early and statistically significant improvement in RLS symptoms compared with placebo recipients; the 16.6-point reduction in mean IRLSSG severity rating scale sum score at week 12 (Sect. 3) corresponded to a clinically significant improvement in symptoms from 'very severe' at baseline to, on average, 'mild or moderate' at the end of the double-blind phase. Interestingly, the magnitude of the treatment effect from weeks 2 through 12 was at least as large as that seen with dopaminergic drugs in the first-line treatment of moderate to severe RLS; hence, head-to-head comparisons of oxycodone/naloxone PR and dopaminergic drugs as first-line treatment are warranted [24]. Longer-term, a beneficial effect of oxycodone/naloxone PR persisted through 1 year of treatment; almost one-quarter of patients were asymptomatic at the end of the open-label extension phase (Sect. 3). Importantly, improvements in RLS symptoms in oxycodone/naloxone PR-treated patients were accompanied by similarly sustained improvements in disease-specific QOL and subjective sleep parameters (Sect. 3).

Oxycodone/naloxone PR was generally well tolerated, with a treatment-related adverse event profile (e.g. gastrointestinal disorders, CNS disorders, fatigue and pruritus) that was consistent with that expected for opioid therapy (Sect. 4). There were no confirmed cases of augmentation or tolerance among oxycodone/naloxone PR recipients throughout the course of the trial (Sect. 4).

Having previously only been approved for the treatment of refractory RLS in Germany [18], oxycodone/naloxone PR has now, by virtue of the RELOXYN study results, been approved for use across many European countries.

Data selection sources: Relevant medical literature (including published and unpublished data) on oxycodone/naloxone as identified by searching databases including MEDLINE (from 1946), PubMed (from 1946) and EMBASE (from 1996) [searches last updated 24 June 2015], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Oxycodone, naloxone, OXN, Targin, opioids, restless legs, Willis-Ekbom, Wittmaack-Ekbom.
Study selection: Studies in patients with restless legs syndrome who received oxycodone/naloxone. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Disclosure The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article. Changes resulting from comments received were made by the author on the basis of scientific and editorial merit. James Frampton is a salaried employee of Adis/Springer.

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