Evidence Table

The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Intervention	Study design	Duration	Administration protocol	Comparison	Diagnostic criteria
Adler, 2004 (48)	Ropinirole	Randomized (1:1), double-blind, placebo-controlled, crossover trial	9 weeks; 4 weeks each plus 1 week washout	Ropinirole 0.5-6.0 mg/day; given in divided doses of 0.25 mg between 6 and 7 PM and at bedtime (total dose 0.5 mg). The does was raised to 1.0 and then 1.5 mg/day every 3 days and then to 2.0, 4.0, and finally 6.0 every 5 days.The subjects remained on 6.0 mg/day for 1 week, for a total treatment period of 4 weeks. If not tolerated, lower doses could be used. The mean dosage was 4.6 (2.0) mg/day, range 1 to 6; 14 patients taking the full 6 mg/day.	Placebo	IRLSSG
Allen, 2004 (53)	Ropinirole	Double-blinded, randomized (1:1), placebo-controlled, parallel-group study.	12 weeks	Flexible dose ropinirole (0.25-4.0 mg/day) or placebo. Medication titrated to an optimal dose, based on the investigator's impression of individual efficacy and tolerability. Therapy was initiated at 0.25 mg/day of ropinirole or matching placebo for 2 days. At Day 2, the dose was then increased to 0.5 mg/day for 5 days. Thereafter, the dose could be increased in 0.5-mg increments at weekly intervals up to 3.0 mg/day, with a final increase from 3.0 mg/day to 4.0 mg/day. A stable dose was to be maintained for the last 4 weeks of the study. Treatment was administered 1 to 3 hours prior to bedtime, depending on patients' symptoms. The mean daily dose at Week 12 was 1.8 mg/day (median 1.5 mg/day) in the ropinirole group, compared with a dose equivalence of 2.7 mg/day (median 3.0 mg/day) in the placebo group. The treatment received by 4 (12.5%) patients in the ropinirole group was titrated to the maximum dose of 4.0 mg/day compared with 12 (36.4%) patients in the placebo group.	Placebo	IRLSSG
Allen, 2010 (92)	Pregabalin	six-arm, double-blind, placebo-controlled, dose–response study randomized	6 weeks	Placebo or pregabalin 50, 100, 150, 300, or 450 mg/day	Placebo	IRLS
Aukerman, 2006 (133)	Exercise	Randomized controlled trial	12 weeks	The exercise group was prescribed a conditioning program of aerobic and lower-body resistance training 3 days per week performed at a hospital-based wellness center.	No exercise/strength training program	IRLSSG severity scale
Baughman, 2009 (125)	Avoidance of specific medications: Antidepressants	Cross-sectional survey design	N/A	N/A	N/A	NIH consensus conferece criteria (Allen 2003) -However, in the current study we used a more stringent case definition for RLS, requiring that cases meet the four criteria and report symptoms at least 5 days per month.
Benes, 2004 (66)	Cabergoline	Open-label intervention study; no control group; multi-center (37)	6 months	Cabergoline was upwardly titrated over 4 weeks to individually optimized dosages. The median daily dose of cabergoline was 1.5 mg (range 0.3 - 8.0).	None	IRLS Study Group criteria
Benes, 2006 (116) ORAL	Dopaminergic, Other agonists: Lisuride	two open-label single-center clinical and PSG studies using identical designs	4 weeks	**Oral lisuride as monotherapy as well as in combination with levodopa**. Daily doses at study end were 0.3mg lisuride, plus 150mg levodopa in the combination study. Lisuride was applied in the same way in both studies: treatment started with a daily evening dose of 0.1mg lisuride. Doses could be increased every other day within the first week according to the patients' needs up to a maximum dose of 0.4mg per day. In the LEV study, levodopa was continued at pre-trial dosage but it was recommended to the investigators to reduce levodopa dose after starting lisuride therapy, if appropriate. Oral lisuride was applied one hour before bedtime in a dose range of 0.1mg and 0.4 mg in the NOV study (mean standard deviation: 0.30± 0.12 mg=day) and in a range between 0.2 mg to 0.4 mg in the LEV study (0.31± 0.09).	None	Idiopathic RLS according to the minimal criteria for RLS of the International Classification of Sleep Disorder (DCSC, 1990: ICSD diagnosis 780.52-5) in moderate or severe intensity and according to the minimal criteria for periodic leg movements of ICSD diagnosis 780.52-4 of any severity level.

Evidence Table
The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Intervention	Study design	Duration	Administration protocol	Comparison	Diagnostic criteria
Benes, 2006 (115) PATCH	Dopaminergic, Other agonists: Lisuride	Initial open-label phase for 2 weeks. Patients were then randomized to double-blind treatment with lisuride (n=5) or placebo (n=4) for 1 week.	3 weeks total	Open label phase: one (n=3 patients) or, if required, two patches of lisuride every other day (dose per patch: 3 mg lisuride, nominal effective release rate 7.0 μg lisuride/h). One single patch was given every other day in the morning preferentially on an abdominal site to deliver lisuride continuously across the skin into the systemic circulation for a period of 48 h during a first week under open conditions, to be doubled (two patches every other day) in the second week if the patient had tolerated this patch during the first week but felt the response was not yet sufficient. Three patients were treated with one patch every other day during both study periods; in the remaining seven patients, lisuride dosage was increased to two patches after 1 week; of those, one patient was not randomized.	Placebo	IRLSSG
Bliwise, 2005 (52)	Ropinirole	Randomized, double-blind, short-term, placebo-controlled clinical trial.	4 weeks open-label titration followed by 2 weeks double blind trial	Mean dose 1.4 mg HS. All medications used to treat RLS were suspended the evening prior to screen/ baseline evaluation. The night of baseline, all patients were initiated on ropinirole, 0.25 mg at bedtime, and entered an open-label dose titration period of 2 weeks, during which ropinirole was titrated gradually to maximal clinical efficacy. Dosage was increased by increments of 0.25 mg up to 1.5 mg, at which point split dosing was instituted with a second (usually smaller) dose given in the early evening. Maximum daily dosage allowed was 6 mg. Subsequent to these 2 weeks of titration, the patients then continued in a sustained (open-label) efficacy period for an additional 2 weeks during which time a constant ropinirole dosage was maintained with repeat assessments during that period. At visit 5, individual patients were randomized to receive either placebo or ropinirole for a 2-week double-blind phase maintaining the dosage achieved during the open-label efficacy phase.	Placebo	Walters 1995 and Allen 2003
Bogan, 2006 (49) **TREAT RLS US Study**	Ropinirole	Randomized (1:1), doubleblind, placebo-controlled, multicenter	12 weeks	0.25-4.0 mg as needed and tolerated, once daily, 1 to 3 hours before bedtime. Mean dose 2.1 (1.2) mg/d. The initial dose of ropinirole or placebo was 0.25 mg/d and could be titrated as needed and tolerated to 0.5 mg/d at the day 3 visit. From day 7 (week 1) onward, the dose could be increased by 0.5 mg/d in weekly increments up to 3.0 mg/d, with a final increase to a maximum of 4.0 mg/d. Down-titration, by 1 dose level, was allowed twice during the first 10 weeks of the treatment period, providing the patient had reached the dosage of 0.5 mg/d and was experiencing an adverse event (AE). If the AE subsided, the dose could be returned to the original higher level at a scheduled clinic visit. No further dose changes could be made after week 10.	Placebo	IRLSSG

Evidence Table

The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Intervention	Study design	Duration	Administration protocol	Comparison	Diagnostic criteria
Bogan, 2010 (89)	Anticonvulsant medications: Gabapentin enacarbil	Single-blind treatment phase followed by a randomized, double-blind phase	24 weeks for SB, followed by 12 weeks DB	SB: Treatment was initiated on days 1 to 3 with one 600-mg extended-release tablet of gabapentin enacarbil. From day 4, patients received gabapentin enacarbil,1200 mg (two 600-mg tablets). DB: Patients randomized to placebo received one 600-mg tablet of gabapentin enacarbil and 1 placebo tablet once daily in a 2-week taper from weeks 24 to 26, followed by 2 placebo tablets from weeks 26 to 36. Blinding was maintained using matching placebo and gabapentin enacarbil tablets and by switching from a single bottle of tablets to 2 bottles with identical packaging 1 month before randomization so that patients did not know when placebo treatment was initiated.Patients randomized togabapentin enacarbil continued to receive gabapentin enacarbil, 1200 mg once daily, during weeks 24 to 36. At the end of the study or after early withdrawal, patients received one 600-mg tablet of gabapentin enacarbil or 1 placebo tablet, according to their treatment schedule, during a 7-day taper.	Placebo	IRLSSG
Braun, 2009 (114) **plus domperidone (In Background section)**	Rotigotine	Randomized, open-label, two-way crossover clinical trial	4-5 days	Treatment A consisted of transdermal rotigotine patch (2mg $(24\ h)^{-1}$, 10 cm^2, total drug content 4.5 mg) applied daily for 4 days, and concomitant oral domperidone (10 mg t.i.d.) for 5 days. For treatment B, subjects received only transdermal rotigotine treatment (daily for 4 days).	Rotigotine without domperidone	N/A
Cuellar, 2009 (124)	Vitamins, minerals, and herb: Iron, magnesium, valerian: **Valerian**	A prospective, triple-blinded, randomized, placebocontrolled, parallel design	8 weeks	Two 400-mg capsules (0.58 mg verenic acid per capsule), total 800 mg valerian vs. placebo, 60 min before bedtime every night. Dry root used (no extraction solvent).	Placebo	IRLSSG
Davis, 2000 (99)	Vitamins, minerals, and herb: Iron, magnesium, valerian: **Ferrous sulfate, oral**	Randomized, Double-Blind Placebo-Controlled Trial	12 weeks, up to 26 weeks if wanted to	**Ferrous sulfate**, 325 bid in liquid form or placebo	Placebo	IRLSSG
Earley, 2004 (103)	Vitamins, minerals, and herb: Iron, magnesium, valerian: **Iron dextran, intravenous**	Open-label	2 weeks post-treatment	We used a single infusion of 1000 mg **iron dextran**. An initial 25 mg was infused, the patient monitored for one hour for allergic reactions, and the remaining 975 mg infused at a rate of about 3–5 mg/min.	None	NIH 2003
Earley, 2009 (101)	Vitamins, minerals, and herb: Iron, magnesium, valerian: **Iron sucrose, intravenous**	Randomized, parallel-group double-blind study	2 weeks post-treatment	1000 mg **iron sucrose given IV** versus placebo. Subjects had infusions (iron or placebo) on day 3 and day 4 with discharge on day 5.	Placebo	Not described
Ehrenberg, 2000 (153)	Valproate	Open label	From 2 weeks to 14 months (median, 5 months; mean, 6 months).	low-dose **valproate** (VPA) treatment (125-600 mg at bedtime).	Baseline	PSG : Leg movements, Atlas Task Force of ASDA Sleep, 1993
Eisensehr, 2004 (123)	Miscellaneous medications: Valproic acid	Randomized, placebo-controlled, double-blind, cross-over study. Efficacy of valproic acid (VPA) compared to that of levodopa (LD).	9 weeks; open label follow-up 6-18 months after the study end	600 mg slow-release **VPA** and 200 mg slow-release LD+50mg benserazid; all patients received placebo, 600 mg slow release VPA and 200 mg slow-release LD (+ 50 mg benserazid), each for three weeks. Doses of VPA/LD were started with 300/100 mg and increased to 600/200 mg after two days. Patients were instructed to take their medication 90 minutes before bedtime.	Levodopa/benserazid and placebo	IRLSSG
Ellenbogan, 2011 (88)	Gabapentin enaacarbil	Open-label, multicenter, 52-week extension study for long-term safety and efficacy	52 weeks, up to 64 weeks	All subjects received gabapentin enacarbil once daily at 5 PM with food for up to 52 weeks. The titration comprised the following: days 1 to 3, one gabapentin enacarbil 600 mg extendedrelease tablet; from day 4, gabapentin enacarbil 1200 mg (two 600 mg extended-release tablets). Dose increases to 1800 mg and decreases to 600 mg were allowed at investigator discretion based on efficacy and tolerability. At the end of the study/ET, subjects receiving gabapentin enacarbil 1200 or 1800 mg began a 7-day downward taper. Subjects completing or terminating at gabapentin enacarbil 600 mg discontinued medication without a taper.	Placebo	Not explicitly stated; probably in parent study reports

Evidence Table
The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Intervention	Study design	Duration	Administration protocol	Comparison	Diagnostic criteria
Ferini-Strambi, 2008 (30)	Pramipexole	Randomized, double-blind, placebo-controlled, flexible-dose, parallel-group design.	12 weeks	Pramipexole (flexibly titrated from 0.25 to 0.75 mg), 2–3 h before bedtime. Patients who met inclusion and exclusion criteria received 0.125 mg pramipexole or placebo (treatment ratio 1:1) 2–3 h before bedtime as the initial dose. Based on efficacy (PGI) and tolerability, the dose could be increased incrementally to 0.25, 0.50, or 0.75 mg at visits or phone calls that occurred over the first 4 weeks of the study: Day 5 ± 1, Day 9 ± 1, Day 14 ± 2, and Day 28 ± 2. After 4 weeks, patients were maintained on their optimal dose for an additional 8 weeks and returned for a clinic visit on Day 84 ± 3 (Week 12) for final assessment. The final dose level achieved in pramipexole-treated patients (ITT population) was 0.125 mg for 15.4% (28/182), 0.25 mg for 33.0% (60/182), 0.5 mg for 26.9% (49/182), and 0.75 mg for 24.7% (45/182).	Placebo	IRLSSG
Garcia-Borreguero, 2002 (91)	Anticonvulsant medications: Gabapentin	Randomized, double-blind, cross-over study	6 weeks / 1 week washout / 6 weeks crossover	Gabapentin was started at a daily dosage of 600 mg, which could be changed at 2 week intervals in 600 mg/day increments up to a maximum dosage of 2400 mg/day. The mean effective dosage at 6 weeks was 1885 mg, although therapeutic effects were already observed at week 4 at 1391 mg. The medication was administered at 12:00 and 20:00, each capsule with 300 mg; 1/3 of daily dosage was taken at 12:00 and 2/3 at 20:00.	Placebo	IRLSSG and PSG
Garcia-Borreguero, 2007 (56)	Ropinirole	Multicentre, open-label continuation study	52 weeks	The mean ropinirole dose at study end was 1.90 mg/day. In this continuation study, all participants received ropinirole, 0.25–4.0 mg once daily, 1-3 h before bedtime. Subjects started treatment at a dose of 0.25 mg/day (day 0), which was titrated upwards through predetermined dose levels (0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 mg/day) to a maximum of 4.0 mg/day or until clinical efficacy had been reached (according to the investigator's discretion, based on weighing therapeutic effect against tolerability). Dose titration could take place on day 2 and day 7 and then no more frequently than every seven days. Dose reduction to the previous dose level because of an adverse event was permitted at any time after day 2, between scheduled visits if necessary.	None (open continuation trial)	IRLSSG
Garcia-Borreguero, 2010 (93)	Pregabalin	Randomized, multicenter, double-blind, placebo-controlled, parallel-group, flexible-dose study	2 weeks single blind period then 12 weeks with flexible dose schedule	The mean effective dose of pregabalin at the end of treatment was 322.50 mg/day (98.77), although therapeutic effects were already seen at a mean dose of 139 mg/day	Placebo	Diagnosis was made through a thorough examination of medical history, followed by a physical examination.
Grote, 2009 (102)	Vitamins, minerals, and herb: Iron, magnesium, valerian: **Iron sucrose, intravenous**	Randomized, double-blind, placebo controlled, multi-center	12 months	Twenty-nine patients received 200 mg **iron sucrose** [10 mL of 20 mg/mL iron (III) as iron sucrose (iron (III)- hydroxide sucrose complex Venofer, Uppsala, Sweden) corresponding to 200 mg iron (III), Vifor, St Gallen, Switzerland] at five occasions evenly spread over 3 weeks. This dosage was chosen to increase S-ferritin concentrations by 80–100 lg/L.Thirty-one patients received placebo (sodium chloride 0.9%, Fresenius Kabi, Germany) at the corresponding time intervals.	Saline	NIH 2003

Evidence Table

The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Intervention	Study design	Duration	Administration protocol	Comparison	Diagnostic criteria
Happe, 2003 (90)	Anticonvulsant medications: Gabapentin	Open clinical trial, randomized treatment, pilot study	4 weeks with follow-up for 6-10 months	**Gabapentin vs. Ropinirole** Either 300 mg of gabapentin or 0.5 mg of ropinirole as the initial dose; up-titrated until relief of symptoms was achieved (gabapentin mean dosage 800 ± 397 mg, range 300–1,200 mg; ropinirole mean dosage 0.78 ± 0.47 mg, range 0.25–1.50 mg) . Gabapentin started with a single dose of 300 mg given 2 h prior to bedtime, increased in steps of 300 mg until RLS symptoms clearly improved or disappeared. If necessary, gabapentin dosages of 600 mg or higher were divided and taken twice a day (in the late afternoon and 2 h prior to bedtime). Ropinirole started with 0.50 mg given as 0.25 mg in the late afternoon and 0.25 mg 2 h prior to bedtime to avoid nausea, and this was increased in steps of 0.25 mg until RLS symptoms clearly improved or disappeared. 6-10 months later, all patients treated with gapabentin were still on gabapentin monotherapy with a mean dosage of 533 ± 328 mg (300–900 mg); for ropinirole, only 3 patients were still on ropinirole monotherapy with a dosage of 0.25, 0.5 and 0.5 mg, respectively.	Ropinirole	IRLSSG
Hayes, 2008 (150)	Endovenous laser ablation	Prospective, randomized, unblinded, parallel two-group, pre-post-test study. COMMENT: DON"T SEE HOW THIS IS RANDOMIZED	6 weeks to f/u exam	Endovenous laser ablation (ELA) of refluxing superficia axial veins using the CoolTouch CTEV 1320 nm laser and ultrasound-guided sclerotherapy of the associated varicose veins with foamed sodicum tetradecyl sulphate (STS). Settings of 50 Hz and 7W. The pullback device was set on 0.5 mm/s for the first 10 cm, then 1.0 mm/s for the remainder of the vein. These laser settings applied 140 J/cm to the first 10 cm of vein, and 70 J/cm to the remainder of the vein (this rather high fluence was utilized to ensure 100% ablation of all treated veins). Varicose veins and refluxing perforator veins were treated with ultrasound-guided sclerotherapy using 1.0% STS foam. A 6-inch ACE wrap was applied immediately postoperatively and continued for 48 h, then replaced with 20–30 mmHg compression stockings for two weeks. Compression was then removed.	Non-operative cohort	2003 NIH RLS criteria
Hening, 2010 (110)	Rotigotine	Randomized, double-blinded, placebo-controlled trial (NCT00135993)	6 months	Placebo or rotigotine (0.5, 1, 2, or 3 mg/24 hr) delivered by once-daily transdermal patch (fixed-dose regimen).	Placebo	IRLSSG
Hogl, 2010 (61)	Levodopa	Prospective, open-label, multi-center	6 months (1 month dose-finding, 5 months maintenance)	Levodopa was flexibly up-titrated to a maximum dose of 600 mg/day. The mean maximum dose of levodopa was 311 mg/day (SD: 105). During the initial dose adjustment period, according to the protocol, levodopa/benserazide had to be up-titrated from 100/25 mg per day to a minimum dose of 200/50 mg per day, but could be further increased to a maximum dose of 600/150 mg per day, although this maximum dose was never reached during the study.	None	IRLSSG
Hogl, 2010 (113)	Rotigotine	Open label extension of SP709	2 years	Mean daily rotigotine dose after 2 years was 2.93 ± 1.14 mg/24 h with a 2.9% dose increase from year 1.	Baseline	IRLSSG
Hornyak, 2008 (130)	Behavioral and Stimulation Therapies: Group therapy	For this pilot study, we performed a pre–post comparison of outcome measures taken at baseline, at an intermediate mid-treatment assessment after 4 weeks, and at the final visit after conclusion of the group therapy as well as at follow-up. There was no control group. Evaluations of outcome parameters were performed by an independent rater who was not involved in any of the therapy procedures. Cannot exclude placebo effects.	8 weeks with 3 month follow up	We developed a psychologically based group therapy approach tailored to the specific aspects of the disorder, with the aim of improving coping strategies and quality of life of patients with RLS (the RELEGS, Restless Legs Skills programme). The programme integrates cognitive behavioural elements and acceptance-based mindfulness approaches. Each group took part in eight weekly group sessions (90 min each with a break).	Baseline	Allen 2003

Evidence Table

The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Intervention	Study design	Duration	Administration protocol	Comparison	Diagnostic criteria
Inoue, 2010 (34)	Pramipexole	Double-blind, placebo-controlled, multi-centre, parallel-group, forced titration study	6 weeks	The study was a 6-week, double-blind, placebo-controlled, multi-centre, parallel-group, forced titration study designed to evaluate the efficacy of pramipexole over a dose range of 0.125–0.75 mg/day by using polysomnographic measures, patient ratings, and a clinical rating in Japanese patients with primary RLS having PLM. After completing baseline assessments, patients were randomly assigned to receive pramipexole or placebo in a 1:1 ratio. For patients randomized to the pramipexole group, the starting dosage of 0.125 mg/day was escalated to 0.25, 0.5, and 0.75 mg/day in weekly steps. All patients took their dose once daily 2–3 h before bedtime.	Placebo	IRLSSG
Inoue, 2010 (38) (Neurology)	Pramipexole	A phase III, open-label, long-term clinical study	52 weeks	Started on pramipexole 0.25 mg/day and were subsequently maintained on that dose or switched to 0.125, 0.5, or 0.75 mg/day to achieve optimal efficacy and tolerability	Baseline	IRLSSG
Jama, 2009 (35)	Pramipexole	Double-blind, placebo-controlled, parallel-group,dose-ranging study	3 weeks	After completing an initial assessment that included polysomnographic evaluation to establish baseline values for all polysomnography-assessed endpoints, patients were randomly assigned to placebo or to one of the pramipexole doses in a 1:1:1:1:1 ratio. Pramipexole therapy was initiated at 0.125 mg and was titrated to the assigned dose in 4-day intervals. The once-daily doses were administered orally 2–3 h before bedtime.	Placebo	See inclusion criteria
Kim, 2008 (126)	Avoidance of specific medications: Mirtazapine	Retrospective review of the available computerized medical records of patients from May 2004 to October 2007.	RLS onset at 1-90 days after mirtazapine treatment began	N/A	N/A	IRLSSG (Allen 2003) Mirtazapine-associated RLS was defined as RLS that was developed or exacerbated after administering mirtazapine and was improved by quitting mirtazapine or adding additional medication for RLS.
Kunz, 2001 (152) **PLMD**	Melatonin	Open clinical trial	6 weeks	3 mg **melatonin**, taken between 10 and 11 p.m. 30 min prior to bedtime	Baseline	ICSD 780.52-4
Kushida, 2008 (54)	Ropinirole	Multicenter, double-blind, randomized (1:1), flexible-dose study	12 weeks	Ropinirole, 0.5 to 6.0 mg/d twice daily in equally divided doses, or placebo. First dose was 1 hour before the usual onset of symptoms; second dose was 3 to 8 hours after the first. All patients initiated therapy at dosage level 1, a total of 0.5 mg/d (two 0.25 mg tablets each day) of ropinirole or matching placebo, which was taken for the first 7 days. Dosage could then be increased (no sooner than every 7 days), one dose level at a time as follows: level 2: 1 mg/d; level 3: 2.0 mg/d; level 4: 4.0 mg/d; and level 5: 6.0 mg/d. Once an optimal therapeutic dose was achieved, the patient was maintained on that dose for the remainder of the study. The mean (SD) ropinirole dose at the end of the study was 3.1 (1.98) mg/d (matched placebo was 4.4 [1.95] mg/d).	Placebo	IRLSSG
Kushida, 2009 (92) **Clinical trials.gov identifier NCT00298623 PIVOT RLS-I**	Anticonvulsant medications: Gabapentin enacarbil	Randomized (1:1), double-blind, placebo-controlled study of XP13512/ GSK1838262	12 weeks	XP13512 1,200 mg or placebo taken once daily at 5:00 PM with food. Patients took one placebo or XP13512 600-mg extended-release tablet on days 1 to 3 and two placebo or 600-mg extended-release tablets on days 4 to 84. Eligible patients then entered an extension study or started a 7-day taper period	Placebo	IRLSSG
Kushida, 2009 (86) **The XP021 Study Group**	Anticonvulsant medications: Gabapentin enacarbil	Randomized, Double-Blind, Placebo-Controlled, Crossover Study	14 days	Xp13512/Gsk1838262 an investigational nondopaminergic agent. XP13512 1800 mg/day followed by placebo or placebo followed by XP13512 1800 mg/day for 14 days, with a 7-day washout between treatment periods. An 1800 mg/ day dose was chosen to produce maximum gabapentin levels of approximately 6-12 µg/mL in the late evening and night.	Placebo	IRLSSG

Evidence Table

The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Intervention	Study design	Duration	Administration protocol	Comparison	Diagnostic criteria
Lauerma, 1999 (78)	Opioid medications: Tramadol	Open	15-24 months	**Tramadol** (central analgesic with fewer side effects and lower abuse potential than classical opioids), 50-150 mg/d	Baseline	Minimum IRLSSG criteria and some of criteria by Gibb and Lees
Lee, 2011 (85)	Gabapentin enaacarbil	Phase III, RCT, DB, multicenter (28 research centers), parallel group, placebo controlled for efficacy and tolerability	12 weeks	600 or 1200 mg GEn 1200 mg (two 600-mg extended release tablets), GEn 600 mg (one 600-mg tablet and one placebo tablet), or placebo (2 placebo tablets), once daily at 5 pm with food	Placebo	IRLS
Lettieri, 2009 (131)	Compression device	Prospective, randomized, double-blinded, sham-controlled trial	1 month	Subjects wore a therapeutic or sham device prior to the usual onset of symptoms for a minimum of 1 h daily. Therapeutic or sub-therapeutic (sham) pressures were used.	Sham device at sub-therapeutic pressure	ICSD-II
Micozkadioglu, 2004 (135)	Gabapentin	Open-label study, randomized, crossover	4 weeks	Levodopa was given in a dose of 125 mg/day to all patients 2 hr before expected sleep onset. Gabapentin was given in a dose of 200 mg after hemodialysis.	Levadopa	IRLSSG
Miranda, 2004 (138)	Pramipexole	Prospective before-after	The mean time of follow-up was 8 months (range 3 to 18 months).	initial dose of 0.125 mg, 2 hours before sleep, with an optional upward titration according to response and tolerance to a maximum daily dose of 0.75 mg, with one dose taken at least 2 hours before dialysis. Domperidone was prescribed to control side effects.	Baseline	IRLSSG
Montagna, 2011 (36)	Pramipexole	Double blind, placebo controlled Phase IV trial	12 weeks	0.125 to 0.75 mg once daily	Placebo	IRLS
Montplaisir, 2006	Pramipexole	Retrospective cohort	Interviews done with patients who were prescribed pramipexole more than 1 year previously	For patients who continued pramipexole: The mean dose of pramipexole was 0.59 ± 0.31 mg and the range was 0.125–2.25 mg; 88 patients (58%) were taking 0.5 mg or less and four patients (2.6%) were taking a dose exceeding 1 mg.	N/A	Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisir J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology –a report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Medicine 2003; 4: 101–119.
Montplaisir, 2006 (55)	Ropinirole	24-weeks titration then randomized to double-blind treatment with ropinirole or placebo for a further 12 weeks.	36 weeks	Ropinirole at an initial dose of 0.25 mg/day, uptitrated after 2 days to 0.5 mg/day, and between weeks 1 and 20, the dose could be increased every 7 days or more to a maximum of 4 mg/day. Titration was guided by the CGI scale efficacy index. Downtitration was allowed if patients experienced AEs, provided the drug dose was ≥ 0.5 mg. Only 2 such dose reductions were allowed before week 20. The patients were instructed to maintain their optimal dose for the remainder of the single-blind treatment phase. Doses were taken 1 to 3 hours before bedtime. Those randomized to ropinirole received the dose that they had established during the single-blind phase; no dose changes were allowed during the double-blind treatment phase. Patients randomized to placebo underwent blinded downtitration of ropinirole over 2 weeks, such that all patients in that group were receiving placebo only from weeks 27 to 36. Furthermore, patients were blinded with respect to the timing of their transition from the single-blind to the double-blind phase.	Placebo	IRLSSG

Evidence Table

The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Intervention	Study design	Duration	Administration protocol	Comparison	Diagnostic criteria
Oertel, 2006 (63)	Cabergoline	A multicenter, double-blind, randomized, placebo-controlled, parallel-group, 5-week PSG study with the two primary endpoints PLMS-AI and sleep efficiency. Randomization used blocks of four patients and was performed at the sponsor's statistical department before patient enrollment. Numbered boxes with study medication were supplied to the study sites. To ensure allocation concealment, patients were assigned by the investigators to one of the two treatments after the medication numbers in ascending order. The blind was not broken before the total trial database had been locked.	5 weeks	Cabergoline (single evening dose: 2 mg at least 3 hrs before bedtime) After baseline assessment, the cabergoline dose was uptitrated in steps of 0.5 mg during study days 1 through 3 (daily dose: 0.5 mg), 4 through 7 (1.0 mg), 8 through 10 (1.5 mg), and 11 through 14 (2.0 mg). On completion of the titration period, a stable dose was administered to all patients for a further 3 weeks. For patients showing inacceptable gastrointestinal side effects after dose increase, domperidone, a peripheral dopamine D2 receptor blocker, could be prescribed.	Placebo	Allen R, Picchietti D, Hening W, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institute of Health. Sleep Med 2003;4:101–119. Walters AS. Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. Mov Disord 1995;10:634–642.
Oertel, 2007 (32) **Effect-RLS Study**	Pramipexole	The study was performed with a double-blind design; at baseline, patients were randomly assigned in a 1:2 ratio to either placebo or pramipexole.	6 weeks	Starting dose of 0.125 mg/day once daily in the evening 2 to 3 hours before bedtime. The dose was individually optimized according to the Patient Global Impression (PGI) assessment, up to a maximum of 0.75 mg/day for up to 4 weeks; weeks 5 and 6 were kept constant.	Placebo	IRLSSG
Oertel, 2008 (107) **Rotigotine SP 709 Study Group**	Rotigotine	A randomized, double-blind, placebo-controlled, dose-finding trial in Europe	6 weeks	Low dosages of 0.5–2 mg/24 h rotigotine as a once-daily transdermal system (patch), was investigated for five fixed dosages and compared to placebo in patients. Each patient was treated with two patches of size 2.5 cm^2 containing rotigotine or placebo and with two patches of size 10 cm^2 containing rotigotine or placebo. By combining patches with active or placebo content, the following dose groups were obtained: 0.5 mg/24 h rotigotine (2.5 cm^2 active patch size; 1.125 mg total drug content), 1 mg/24 h rotigotine (5 cm^2; 2.25 mg total drug content), 2 mg/24 h rotigotine (10 cm^2; 4.5 mg total drug content), 3 mg/24 h rotigotine (15 cm^2; 6.75 mg total drug content), 4 mg/24 h rotigotine (20 cm^2; 9.0 mg total drug content), and placebo.	Placebo	IRLSSG
Oertel, 2008 (112) **Rotigotine SP 710 Study Group**	Rotigotine	Open extension of preceding 6-week SP709 trial	1 year	The mean daily dose was 2.8 ± 1.2 mg/24 h with 4 mg/ 24 h (40.6%) being the most frequently applied dose; 14.8% were sufficiently treated with 0.5 or 1.0 mg/24 h. Rotigotine transdermal patch (0.5–4 mg/24 h) was administered once-daily in the morning without using the same application site twice within 14 days of treatment. In the titration phase of a maximum of 4 weeks duration, patients started with a dose of 0.5 mg/24 h (patch size 2.5 cm^2). The dose could be increased up to a maximum dose of 4 mg/24 h (patch size 20 cm^2) according to the individual needs of the patients with intermediate steps of 1 mg/24 h, 2 mg/ 24 h or 3 mg/24 h.	None (open continuation trial)	N/A
Oertel, 2010 (111)	Rotigotine	Double-blind, randomized, placebo-controlled, multicenter study (NCT00275236).	4 weeks	rotigotine (maximum 3 mg/24 h) or placebo patches once-daily during a 4-week maintenance period	Placebo	IRLSSG
Ondo, 2005 (80)	Opioid medications: Methadone	Retrospective record review, interviews	4-44 months (23±12)	The initial dose of **methadone** at the first follow-up visit was 13.0±5.9 mg/day (range, 5–30 mg/day) and the final dose was 15.5± 7.7 mg/day (range, 5–40 mg/day), usually in two equal doses.	Baseline	IRLSSG, NIH

Evidence Table

The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Intervention	Study design	Duration	Administration protocol	Comparison	Diagnostic criteria
Ondo, 2010 (104)	Vitamins, minerals, and herb: Iron, magnesium, valerian: **Iron dextran, intravenous**	Open label, retrospective	up to 60 weeks	All subjects underwent an infusion protocol totaling one gram of high molecular weight **iron dextran** (Dexferrum , American Regent) over 4–5 h following a 50 mg test dose to assess for allergic reactions. Patients were allowed epinephrine and diphenhydramine if hypotension or other worrisome signs developed. Patients had a pre-infusion serum ferritin, and some had 4–8 week post infusion ferritins. As clinically justified, additional identical infusions were given.	none	IRLS
Partinen, 2006 (33) **PRELUDE Study**	Pramipexole	Double-blind, placebo-controlled, parallel-group, fixed-dose trial	3 weeks	To evaluate the dose effects of pramipexole salt (0.125, 0.25, 0.50, and 0.75 mg/d, where 0.125 mg salt is equivalent to 0.088 mg base). After completing baseline assessments, patients were randomly assigned to 1 of 4 dose levels of pramipexole or to placebo in a 1:1:1:1:1 ratio. All participants randomized to active drug were started on 0.125 mg/d and titrated up to their assigned dose in 4-day intervals. They stayed on their assigned dose until the end of week 3. Doses were taken once daily 2–3 h before bedtime.	Placebo	IRLSSG
Partinen, 2008 (39)	Pramipexole	Open-label	26 weeks	The study's initial, three-week double-blind phase [8] was followed by a one-week washout and then by its second phase, reported here: a 26-week, open-label trial designed to evaluate the treatment's long-term efficacy and safety. After each of the first three open-label weeks, pramipexole initiated at 0.125 mg/day was incrementally adjustable, so as to attain a satisfactory maintenance level (0.125, 0.25–0.375, 0.50–0.625, or 0.75 mg/day, in which 0.125 mg salt is equivalent to 0.088 mg base). Each titration decision was based on the individual's Patient Global Impression (PGI) self-rating (see under Section 2.4), in accordance with the investigator's judgment, and at all times, both patient and investigator were aware of the dosage level. All patients were instructed to take their medication once daily, between 8 and 9 p.m.	Baseline	IRLSSG
Pellecchia, 2004 (137)	Ropinirole vs levodopa sustained release	Open randomized crossover	14 weeks: 1 week screening, treatment 6 weeks, followed by a washout week, then the alternate treatment for 6 weeks.	Ropinirole vs. levodopa sustained release (SR). By the end of the study the mean levodopa SR dosage was 190 mg/d and the mean ropinirole dosage was 1.45 mg/d. Patients were given evening doses of ropinirole or levodopa SR, 2 hours before bedtime. Ropinirole was begun at the 0.25-mg/dose. Doses could be doubled every 5 days during the first 2 weeks and then increased up to 2 mg/dose until symptoms satisfactorily resolved or adverse events became evident. Levodopa (slowrelease levodopa/carbidopa) titration scheme started with 25/100-mg/dose. Doses could be doubled after 2 weeks according to the investigators' and patients' opinions.	Levodopa	Allen RP, Hening WA, Montplaisir J, et al. Restless legs syndrome: diagnostic criteria, special considerations and epidemiology: a report from the RLS Diagnosis and Epidemiology workshop at the National Institutes of Health. Sleep Med. 2003;4:101–119.
Polo, 2007 (60)	Levodopa	Prospective, randomized, double-blind, crossover study with polysomnography.	5 randomized 2-day study periods with a 4- to 8-day washout period in between.	We assessed whether a new levodopa formulation containing levodopa, carbidopa, and entacapone (LCE) improves levodopa action in RLS. Single doses. Study treatments were administered with 200 mL water approximately half an hour before the patient's usual bedtime (between 10 pm and 12 midnight).	Stalevo 50 (LCE50; 50/12.5/200 mg), Stalevo 100 (LCE100; 100/25/200 mg), Stalevo 150 (LCE150; 150/37.5/200 mg), Sinemet 100 (LC100; 100/25 mg), or placebo	IRLSSG

Evidence Table
The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Intervention	Study design	Duration	Administration protocol	Comparison	Diagnostic criteria
Rottach, 2008 (127)	Avoidance of specific medications: Second generation antidepressants (fluoxetine, paroxetine, citalopram, sertraline, escitalopram, venlafaxine, duloxetine, reboxetine, and mirtazapine).	Prospective naturalistic trial	Median 44 days	N/A	N/A	RLS CRITERIA • An urge to move the legs, accompanied or caused by uncomfortable unpleasant sensations in the legs • The urge to move or unpleasant sensations beginning or worsening during periods of inactivity such as lying or sitting, • The urge to move or unpleasant sensations partially or totally relieved by movement such as walking or stretching, • The urge to move or unpleasant sensations worsening or only occurring in the evening or at night.
Sakkas, 2008 (139)	Exercise	Assigned, according to their will, to either the exercise group (Ex-group, n = 7), and participated ina 16-week supervised intradialytic aerobic exercise training, or to the control group (Con-group, n =7), and continued usual activities.	16 weeks	Exercise: aerobic training three times a week during the HD session.	Control who continued usual activities	Walters IRLS 1995
Saletu, 2001 (121)	Benzodiazepines (and other sedative hypnotics): Clonazepam	Single-blind, placebo-controlled, unbalanced cross-over design study.	3 nights: one adaptation night, one placebo night and one drug night	Oral dose of 1 mg clonazepam (Rivotril). Due to the long elimination half-life of clonazepam (t½ 20–60 h), placebo had to be administered first. The drug and placebo were given orally at bedtime (22:30 h).	placebo	RLS: ICD-10 (G 25.8), PLMD ICD-10 (G 25.3); ICSD 78052-2 ASDA and IRLS 1995; ICSD 780.52-4 ASDA
Saletu, 2002 (41)	Pramipexole	The study was performed in two parts: Part one was an acute, single-blind, placebo-controlled, unbalanced crossover trial (randomization not mentioned explicitly) Part two consisted of an open follow-up period over 4 weeks	4 weeks	Part 1: three sleep laboratory nights: a pre-treatment night, a placebo night and a drug night with an evening (9.00 p. m.) dose of 0.088 mg and a bedtime (10.30 p. m.) dose of 0.18 mg pramipexole. The split dose was chosen for reasons of tolerability and in order to be able to compare the data obtained with those of other dopaminergic compounds. Part two consisted of an open follow-up period over 4 weeks,during which the optimal daily dose was titrated stepwise by 0.088 mg in weekly intervals.At each dosage increase, patients were instructed to go back to the previous dosage if they experienced persistent side-effects related to the medication. In the acute single-blind, placebo-controlled part of the study, each patient received a night-time dose of 0.27mg pramipexole. In the subsequent open titration phase, 5 patients remained on their initial dosage. Two patients reduced the dosage to 0.088mg. Three patients increased pramipexole to 0.45mg. Thus, after 4 titration weeks the mean dose of pramipexole was 0.28±0.1mg.	Placebo	ICD-10 G25.8 and ICSD 780.52-5 and IRLS 1995

Evidence Table
The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Intervention	Study design	Duration	Administration protocol	Comparison	Diagnostic criteria
Saletu, 2003 (58)	Levodopa	The study was performed in two parts: Part one was a double-blind, placebo-controlled, acute randomized crossover trial.Patients fulfilling the inclusion criteria were assigned a consecutive study number and were accordingly randomized to one of the two treatment sequences: either first placebo and then combination treatment or vice versa, i.e. first combination treatment and then placebo. Part two consisted of an open follow-up period over 4 weeks.	Part 1: 3 nights (one adaptation, one placebo, and one drug night); 4 weeks open trial	The acute efficacy of a combination treatment of 100mg regular-release (rr) and 100mg sustained-release (sr) L-dopa/benserazide. Rr-L-dopa/benserazide (or a placebo tablet) was given one hour before bedtime (21.30), while sr-L-dopa/benserazide (or a placebo capsule) was given at bedtime (22.30). The optimal daily dose was titrated stepwise in weekly intervals and could be increased to up to two tablets/capsules per night of either 100 mg rr-L-dopa/benserazide or 100mg sr-L-dopa/benserazide (i.e. up to a maximum dosage of 400 mg L-dopa). In the subsequent open titration phase, 9 patients remained on their initial dosage. Two patients reduced the dosage of rr-L-dopa to 50mg, one patient was satisfied with a single dose of 100 mg sr-L-dopa. Three patients increased rr-L-dopa to 150mg, two to 125mg. Only two patients increased the initial sr-L-dopa dose to 200mg to achieve a greater clinical effect. Thus, after 4 titration weeks the mean dose of rr-L-dopa was 100mg ± 38.5, that of sr-L-dopa 112mg ± 33.2.	Placebo	ICD-10, ICSD, IRLSSG
Shinno, 2010 (122)	Pramipexole vs. clonazepam	Prospective, open-label, multicenter study	2-5 weeks	If patients had been prescribed less than 1 mg/day of clonazepam, clonazepam was discontinued and pramipexole was prescribed. The initial daily dose of pramipexole was calculated using a conversion of 1:4 for clonazepam dose. However, if the patients had been prescribed 1 mg/day or over 1 mg/day of clonazepam, two protocols for switching were adopted (Fig. 1B). One protocol was the rapid switch, which was the same as for patients pretreated with a lower dose of clonazepam (Fig. 1B-(a)). The other was gradual switching. Intermediate doses of clonazepam and pramipexole were prescribed for a week followed by a complete switch to pramipexole (Fig. 1B-(b)). As RLS symptoms and adverse effects were observed, the dose of pramipexole was titrated. The daily dose of pramipexole was up titrated or tapered by 0.125 mg/day at each subsequent examination.	clonazepam	IRLSSG
Silber, 2003 (43)	Pramipexole	Retrospective record review	The mean duration of follow-up for the remaining 49 patients (who did not discontinue use in less than 4 months) was 27.2 months (range 4-46 months).	The median daily dose increased from 0.38 mg after stabilization to 0.63 mg at the end of the study. By the end of the study, 14 patients (29%) were taking the drug twice a day, with the first dose usually in the afternoon or early evening. Four patients (8%) required pramipexole 3 times a day, 3 taking it in the morning, afternoon, and before bed, and 1 taking it in the early afternoon, early evening, and before bed. Nineteen patients (39%) had not needed to increase the dose at all.	N/A (retrospective review)	IRLSSG
Sloand, 2004 (136)	Iron dextran, intravenous	Random, double-blind placebo controlled trial	4 weeks	1000 mg intravenous (IV) iron dextran or saline. Both placebo and drug were infused during dialysis by infusion pump with the medication (or placebo) and tubing covered with an opaque obscuring sleeve so that neither the patient, investigator, nor study nurse could detect which was being administered.	Placebo (saline)	IRLSSG
Sommer, 2007 (149)	Pregabalin	Cohort	Mean duration of 217 (standard deviation, 183) days	Titrated **pregabalin** as licensed with 75 mg b.i.d., with one dose in the early afternoon and one dose in the evening, and increased or reduced the dosage according to the patient's needs. Mean daily dose of 305 mg (standard deviation, 185 mg)	Baseline	Not stated

Evidence Table

The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Intervention	Study design	Duration	Administration protocol	Comparison	Diagnostic criteria
Stiasny-Kolster, 2004 (64)	Cabergoline	The study was based on a prospective, multicenter, double-blind, randomized, placebo-controlled, parallelgroup design (period I) for the dose-finding period followed by an open long-term extension. The blinded dose-finding period (I) lasted 5 weeks and consisted of a 3-week titration-phase and a 2-week maintenance period with stable dosing. Patients who completed period I of the study were allowed to participate in an open long-term extension trial with a duration of 47 weeks, which was divided in two treatment periods (open titration period = period II, long-term treatment period = period III). For the open titration period (II) no time frame for the process of dose titration was given in the protocol.	52 weeks total: 5 weeks of Period 1 dose-finding and 47 weeks of open label extension	Patients were randomly assigned to receive either a treatment with placebo or with cabergoline in three different dosages (target dose 0.5, 1.0, and 2.0 mg/day). Medication was taken once daily in the evening, at least 3 hours before bedtime.During the first three titration weeks, the study medication was uptitrated following a standardized titration scheme (until the target dose of 0.5 mg, 1.0 mg, or 2.0 mg cabergoline was achieved) starting with 0.5 mg and increasing the dosage by 0.5 mg after 3 days and, if applicable, again by 0.5 mg cabergoline after 4 and further 7 days. Mean CAB dose of 2.2 mg per day.	Placebo for dose-finding trial	Idiopathic RLS diagnosed by history and clinical assessment according to the international diagnostic criteria
Stiasny-Kolster, 2004 (42)	Pramipexole	Open clinical trial	1 week baseline "and when satisfactory relief of RLS symptoms was reported by the patient." "Short-term"	A single dose of 0.125–0.75 mg pramipexole (mean 0.3 ± 0.2 mg) in the evening at least 2 hr prior to bedtime. The initial therapy consisted of one 0.125-mg tablet (pramipexole HCl). Patients could increase the dosage in steps of 0.125 mg if they thought that their RLS symptoms, including sleep impairment, had not sufficiently improved.	None	Not described
Stiasny-Kolster, 2004 (108)	Rotigotine	Double-blind, randomized, parallel-group, multicenter, proof-of-principle trial.	1 week	Three fixed doses of rotigotine (1.125 mg, 2.25 mg, and 4.5 mg) and placebo were applied by patches (size, 2.5 cm^2 per 1.125 mg). Four patches of 2.5 cm^2 containing 1.125 mg of rotigotine or placebo were used to treat the patients with daily doses of 1.125 mg, 2.25 mg, or 4.5 mg of rotigotine, or placebo. No dose titration was performed. The first patches were attached to the right or left upper or lower abdomen after randomization in the evening of the first treatment day; the subsequent patches were exchanged every morning (after 24 hours) on alternating areas of the abdomen.	Placebo	IRLSSG 1995
Thorp, 2001 (134)	Gabapentin	Randomized, double-blind, placebo-crossover study	6 weeks, 1 week washout, 6 weeks of other treatment	200-300 mg gabapentin after each hemodialysis session 3x weekly.	Placebo	Based on IRLSSG
Trenkwalder, 2003 (59)	Levodopa	Open-label, prospective, extension study of a preceding double-blind crossover trial	12 months (treatment average of 10 months)	Combination of RR and SR levodopa; mean daily dose of 203 ± 101 mg of RR and of 185 ± 93 mg of SR levodopa. The mean daily total dose was 388 ± 162 mg levodopa.	None	See previous article 1999
Trenkwalder, 2004 (62)	Pergolide	Phase 1: Double-blind placebo-controlled, randomized trial Phase 2: Open-label (non-responders in Phase 1)	6 weeks (phase I); 12 months (phase 2)	Phase 1: 0.25 to 0.75 mg in the evening (or placebo) 2 hrs before bedtime Phase 2: open-label pergolide up to 1.5 mg/d higher doses taken in divided form 4 and 2 hours before bedtime. Because pergolide is known to cause nausea, domperidone (60 mg/d) was considered necessary during phase 1 to maintain blinding, and was optional during phase 2. Mean dose at end of phase 1 was 0.4±0.18 mg/d; mean dose in double blind pergolide group at 6 months was 0.48±0.2 mg/d and 0.52±0.22 at 12 months. Mean dose in open label are were 0.68±0.55 mg/d at 6 months and 0.72±0.42 at 12 months.	Placebo	IRLSSG

Evidence Table

The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Intervention	Study design	Duration	Administration protocol	Comparison	Diagnostic criteria
Trenkwalder, 2004 (50) **TREAT RLS 1 Study**	Ropinirole	Prospective, double blind, randomised (1:1) comparison involving patients from 10 European countries.	12 weeks	Ropinirole 0.25–4.0 mg once daily or placebo; week 12 ropinirole (mean (SD) dose, 1.90 (1.13) mg/day). Patients received treatment once daily between 1-3 hours before bedtime and started ropinirole treatment at 0.25 mg/day. The dose was then titrated upwards during weeks 1 to 7, through 7 predetermined dose levels, until patients were receiving the maximum dose (4.0 mg/day) or they were judged to have reached their optimal dose. A maximum of 2 dose reductions because of adverse events (by one dose level in each case) was permitted during the titration period. The dose could be increased again if adverse events ameliorated. Dose changes were not permitted after week 7.	Placebo	IRLSSG
Trenkwalder, 2006 (44)	Pramipexole	The trial was a Phase 3 randomized, double-blind, parallel-group, placebo-controlled (in a 1:1 ratio), multicenter pramipexole withdrawal study of 3 months' duration.	After 6 months and to 9 months (3 months total)	Pramipexole at an individually optimized dose of 0.125 to 0.75 mg/day. During a preceding 6-month period (Period 1), open-label pramipexole was up-titrated to individually optimized dosage (0.125, 0.25, 0.50, or 0.75 mg once daily). All patients were instructed to take their medication 2 to 3 hours before anticipated bedtime.	Placebo	IRLSSG
Trenkwalder, 2007 (67) CALDIR Trial	Cabergoline	Cabergoline vs. levodopa a multi-center, international, double-blind, randomized, active-controlled, parallel-group study	6 weeks with some 30 week data	Fixed daily doses of 2 or 3 mg CAB or 200 or 300 mg levodopa. The daily cabergoline dose was up-titrated after baseline assessment in 0.5 mg increments to 2.0 mg until day 14 whereas L-dopa was increased in steps of 50 mg, 100 mg, and 200 mg until day 8. The cabergoline dose was given 3 hours before bedtime, L-dopa was applied in two doses; the first one (50 or 100 mg) was taken 3 hours before bedtime, the second dose (150 or 200 mg) was administered at bedtime.	Levodopa	IRLSSG
Trenkwalder, 2008 (109) **ClinicalTrials.gov number NCT00136045**	Rotigotine	Randomised, double-blind, placebo-controlled trial	6 months (plus 3 week titration phase, 1 week taper phase, and 4 weeks safety follow-up)	Transdermal rotigotine 1 mg over 24 h, 2 mg over 24 h or 3 mg over 24 h, or placebo from different combinations of two differently sized patches, to give a total drug content in the three treatments of 2·25 mg, 4·5 mg, and 6·75 mg, respectively. Study medication was delivered via patches, applied once a day. Patients were instructed to rotate the application site (abdomen, thigh, hip, flank, shoulder, upper arm) on a daily basis to minimise application-site reactions. All patients in the rotigotine groups started titration with a daily dose of 1 mg over 24 h, which was increased in weekly increments of 1 mg over 24 h to their assigned trial dose. Dose adjustments were not allowed during the maintenance phase.	Placebo	IRLSSG
Walters, 2001 (79)	Opioid medications: General	Retrospective record review	20/36 patients who were ever on monotherapy remained on monotherapy at the time of the survey for an average of 5 years 11 months (range, 1-23 years). 16 patients originally on opioid monotherapy stopped using opioids as a sole therapy after an average of 10.8 months (range, 1 week to 5 years)	The opioids most commonly used in Europe were tilidine, 25 mg (27 trials in polytherapy patients and six trials in monotherapy patients) and dihydrocodeine 60 mg (six trials in polytherapy patients and two trials in monotherapy patients). Those opioids most commonly used in the United States were oxycodone, 5 mg (30 trials in polytherapy patients and 10 trials in monotherapy patients), codeine, 30 mg (16 trials in polytherapy patients and eight trials in monotherapy patients), propoxyphene, 65 mg or N-100 mg (19 trials in polytherapy patients and six trials in monotherapy patients), or methadone, 10 mg (five trials in polytherapy patients and eight trials in monotherapy patients). Typically, between 1 and 4 tablets per day in divided dosages were prescribed, with the bulk of the dose used in the evening when symptoms are maximum	None	RLS was diagnosed initially by criteria devised by the American Sleep Disorders Association with more recent patients diagnosed by criteria delineated by the International Restless Legs Syndrome Study Group (IRLSSG).

Evidence Table

The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Intervention	Study design	Duration	Administration protocol	Comparison	Diagnostic criteria
Walters, 2004 (51) **TREAT RLS 2 Study**	Ropinirole	Double-blind, randomized, parallel-group, placebo-controlled, multinational study	12 weeks	Ropinirole (0.25– 4.0 mg/day) or placebo, 1 to 3 hours before bedtime. The initial dose of ropinirole or matched placebo was 0.25 mg/day. The dose could be titrated after 2 days to 0.5 mg/day. From week 1 through week 7, the dose could be up-titrated by 0.5 mg/day in weekly increments up to 3 mg with a final increase from 3 to 4 mg/day. The flexible titration was guided by the results of the Clinical Global Impression (CGI) scale30 and tolerability. No further drug titration was allowed after week 7. During the titration period, down-titration was allowed twice if patients experienced adverse events, provided the drug dose was at least 0.5 mg/day. A higher dose could be reinstated if the adverse event abated. Only two such dose reductions were allowed before week 8. From weeks 8 to 12, patients maintained a constant dose of ropinirole or placebo.	Placebo	IRLSSG
Walters, 2009 (84)	Anticonvulsant medications: Gabapentin enacarbil	double-blind, randomized, controlled trial	14 days	GEn at 1200 or 600 mg or matching placebo. All study medication was to be taken at 5:00 PM with food. On the first 2 days of treatment, subjects took 1 placebo or 600-mg of GEn extended-release tablet; on the remaining treatment days, subjects took either 2 placebo tablets, 1 placebo tablet and one 600-mg GEn extended-release tablet, or two 600-mg GEn extended-release tablets. Reductions in dose due to tolerability were permitted at the discretion of the investigator.	Placebo	IRLSSG
Wang, 2009 (100)	Vitamins, minerals, and herb: Iron, magnesium, valerian: **Ferrous sulfate, oral**	randomized, placebo-controlled, double-blinded study	12 weeks	Eligible patients were randomized to either oral iron therapy (**ferrous sulfate** 325 mg twice daily, placed in non-descriptive capsules) or an appearance-matched placebo (lactose). A clinical investigative pharmacist, independent from the study, grouped patients using a randomly generated sequenced number program. The clinical investigative pharmacist held the randomization code in a locked cabinet until the end of the study. All patients were also asked to take vitamin C 100 mg orally twice daily.	Placebo-lactose	NIH
Winkelman, 2004 (46)	Pramipexole	Retrospective assesement	At least 6 months (mean duration = 21.2 ± 11.4 months, range 6-60 months)	Pramipexole dosing and clinical follow-up were performed in a standardized fashion. Baseline stable dose and timing of pramipexole administration was defined when adequate control of RLS symptoms was reported, which usually occurred on the first visit following initial pramipexole administration (most commonly 8 weeks after medication initiation). Pramipexole was initiated at 0.125–0.25 mg, 2 h before symptom onset. L-Dopa was discontinued once pramipexole was initiated. Pramipexole dose was increased by 0.125–0.25 mg every 4–7 days at the patient's discretion until symptoms were eliminated or nearly completely relieved. In five patients, augmentation continued to evolve over time, with a need to administer pramipexole earlier and earlier.	N/A (retrospective review)	IRLSSG
Winkelman, 2006 (31) **PIRLS Study**	Pramipexole	Double-blind, randomized, placebo-controlled trial	12 weeks "intermediate term"	Fixed doses of pramipexole (0.25, 0.50, and 0.75 mg/day); uptitrated to dose over 3 weeks. All patients were instructed to take their study medication each evening 2 to 3 hours before anticipated bedtime.	Placebo	IRLSSG

Evidence Table

The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Intervention	Study design	Duration	Administration protocol	Comparison	Diagnostic criteria
Zucconi, 2003 (65)	Cabergoline	single blind ,open labeled clinical trial	2 month	Upward titration of cabergoline (from 0.5 mg to 2 mg) in a single evening dose. (mean dose, 1.1 mg) In a blinded fashion, patients received placebo or cabergoline, starting at 0.5 mg, 2 hours before bedtime and titrated the dose to effectiveness in incremental step of 0.5 mg with a maximum dose of 2 mg.	Placebo	IRLSSG criteria. All patients underwent neurologic examination, electromyography and nerve conduction studies of the lower limbs, laboratory examinations including serum ferritin and iron levels, and 1 night of polysomnography to exclude other pathologies (such as sleep apnea) and to confirm the presence of PLMS. All patients also completed the IRLSSG Rating Scale at baseline (B)

Evidence Table
The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Inclusion/ Exclusion criteria	RLS Severity	Sample size (completed) / mean age (age range or standard deviation) / gender of subjects	Adverse effects	Outcome measures / results	Conclusions	Comments
Adler, 2004 (48)	Patients ≥ 20, RLS rating score ≥ 10. Exclusions: previous use of ropinirole, secondary RLS, significant medical disease that would not allow the use of ropinirole, inability to complete diary forms, pregnancy or lactation.	IRLS≥10 (at least mild)	22 (22) / 60 (SD=13), range 40-83) / 16F 6M	Nausea and dizziness	The primary outcome measure was the change in the RLS rating scale score. Secondary measures included a global change score, ESS, and RLS symptom diary. The RLS Rating Scale score improved (p<0.001) from a mean (SD) 25 (7) during placebo treatment to 13 (12) during ropinorle treatment. Baseline ESS = 8.5 (5.8); ropinirole 6.9 (7.2); placebo 8.1 (6.3) p=ns. Global change scores: ropinirole 1.9 (1.7) and placebo -0.3 (1.7), p<0.001. Diary, mean rate of RLS symptoms: ropinirole 12% (16%) and placebo 23% (15%), p=0.008, 50% reduced. Eight of the 22 patients had complete resolution of symptoms on ropinirole.	Ropinirole was effective and well-tolerated for treating the symptoms of RLS. The degree of improvement was approximately 50% using the RLS Rating Scale and diary data.	
Allen, 2004 (53)	Inclusions: Patients with RLS and PLMS, 18 and 79 years old, 5 PLMS/h, a score of ≥15 (moderate severity) on the IRLS at baseline, a minimum of 15 nights with RLS symptoms in the month prior to the study. Exclusions: daytime RLS symptoms requiring treatment, sleep disorders other than RLS, movement disorders, signs or symptoms of secondary RLS (eg, secondary to pregnancy, renal failure, iron-deficiency anemia, gastric surgery, or neuropathy), any unstable medical conditions (eg, severe cardiovascular disease or orthostatic hypotension), or conditions that could affect efficacy assessments (eg, diabetes, peripheral neuropathy, rheumatoid arthritis or fibromyalgia syndrome). Patients who had oxygen saturation values < 80% at any time during the night or had more than 5 significant sleep disordered breathing events per hour of sleep on the screening PSG. Significant sleep-disordered breathing events were defined as apneas or hypopneas lasting for at least 10 seconds with a minimum of an 8% decrease in oxygen saturation.	IRLS≥15 (moderate severity at minimum)	65 (55) / Ropinirole: 55.4 (10.3) Range 37-76; Placebo: 53.3 (12.5) Range 30-79 / Ropinirole: 17F12M; Placebo: 17F13M	No serious adverse events occurred in either group. The most common adverse events reported during treatment were headache (occurring in 34.4% of the ropinirole group versus 18.2% of the placebo group) and nausea (31.3% in the ropinirole group versus 15.2% in the placebo group). Dizziness, vomiting, and hyperkinesias were reported by more than 10% of the patients receiving ropinirole. Somnolence also exceeded 10% in both groups and was similar between groups (15.6% in the ropinirole group versus 12.1% in the placebo group). One patient in the ropinirole group withdrew from the study due to an adverse event (worsening of headache). Five patients (4 in the ropinirole group and 1 in the placebo group) experienced worsening of RLS symptoms, which were coded as hyperkinesias.	PLMS/hr decreased more with ropinirole (48.5 to 11.8), compared with placebo (35.7 to 34.2; adjusted treatment difference [ATD]: -27.2; 95% CI: -39.1,-15.4; P < .0001). Periodic limb movements with arousal per hour decreased from 7.0 to 2.5 with ropinirole but increased from 4.2 to 6.0 with placebo (ATD: -4.3, 95% CI: -7.6,-1.1; P = .0096). Periodic limb movements while awake per hour decreased from 56.5 to 23.6 with ropinirole but increased from 46.6 to 56.1 with placebo (ATD: -39.5; 95% CI: -56.9,-22.1; P < .0001). Ropinirole treatment significantly improved patients' ability to initiate sleep (P < .05) and the amount of Stage 2 sleep compared with placebo (P < .001). There were also nonsignificant trends toward increases in total sleep time and sleep efficiency. Sleep adequacy (measured on the subjective Medical Outcomes Study sleep scale) was significantly improved with ropinirole treatment (ATD: 12.1; 95% CI: 1.1,23.1; P = .0316). In contrast, the placebo group showed a greater increase in Stage 3/4 sleep (P < .01).	Ropinirole is effective in the treatment of both the sleep and waking symptoms of RLS.	
Allen, 2010 (92)	Patients18-65 years, male and female, Patients were excluded if they had any form of secondary RLS, severe daytime symptoms (e.g., requiring regular medication treatment), a present or past history of another severe sleep disorder (e.g., Apnea/Hypopnea Index >20) by medical history and/or clinical evaluation; more in paper	Moderate-to-severe idiopathic RLS	137 / about 50 (not reported for entire cohort) / female percent ranged from 56 to 79	Dizziness and somnolence were the most common adverse events and appeared to be dose-related.	The primary endpoint, the change in the International Restless Legs Study Group Rating Scale (IRLS) total score from baseline to week 6 of treatment. Secondary outcomes included Clinical Global Impressions-Improvement Scale (CGI-I) responders, sleep assessments, and safety. Placebo resonse was -7-7±8.2; 150 mg/day was -16.0±8.9; 300 mg/day was -12.9±8.3; and 450 mg/day was -16.3±8.6 A higher proportion of CGI-I responders was observed at the two highest doses of pregabalin (300 and 450 mg/day) versus placebo.	In this 6-week phase 2b study, pregabalin reduced RLS symptoms in patients with moderate-to-severe idiopathic RLS. The symptom reduction at week 6 was dose-dependent with 123.9 mg/day providing 90% efficacy. Pregabalin was safe and well tolerated across the entire dosing range.	
Aukerman, 2006 (133)	Participants were excluded from this study for the following reasons: orthopedic condition that limited ambulation on a treadmill or ability to perform prescribed resistance exercises, recent coronary event in the preceding six months, uncontrolled hypertension, renal dysfunction (serum creatinine greater than 1.5 mg/dL) or anemia (hemoglobin < 13 g/dL in males and < 11 g/dL in females).	From data, moderate to severe	28 (23) / (average age 53.7; 39% males)	None reported	Restless legs symptoms were assessed by the International RLS Study Group (IRLSSG) severity scale and an ordinal scale of RLS severity at the beginning of the trial, and at 3, 6, 9, and 12 weeks. The exercise group (N = 11) had a significant improvement in symptoms compared with the control group (N = 12) (P < .001 for the IRLSSG severity scale and P < .001 for the ordinal scale).	The prescribed exercise program was effective in improving the symptoms of RLS.	Participant recruitment was accomplished via television advertisements, notices in local newspapers, and flyers placed in patient areas of an academic medicine primary care clinic.
Baughman, 2009 (125)	Study participants were veterans who had scheduled primary care visits at one of the twelve CBOCs between June 2003 and August 2004. Participants were required to be age 18 or older, non-institutionalized, competent to give informed consent, and able to be interviewed in English.	Not described	6624 eligible; 2714 approached; 2112 informed consent; 1761 completed interview; 1693 complete data /20-39=140, 40-59=615, 60-79=572, 80+=366 /W329 M1364	N/A	Overall, use of an antidepressant was associated with RLS for men (RR=1.77, CI=1.26, 2.48) but not for women (RR=0.79, CI=0.43, 1.47). Analyses of individual antidepressants revealed an association betweenRLS and fluoxetine for women (RR=2.47, CI=1.33, 4.56), and associations between RLS and citalopram, (RR=2.09, CI=1.20, 3.64), paroxetine (RR=1.97, CI=1.02, 3.79), and amitriptyline (RR=2.40, CI=1.45, 4.00) for men	We conclude that RLS may be associated with antidepressant use, but the association varies by gender and type of antidepressant. Antidepressant use is more strongly associated with RLS in men than in women.	
Benes, 2004 (66)	IRLS patients at least 18 years of age; meeting all 4 diagnostic criteria of the IRLSSG Exclusions: (1) signs or symptoms indicating the presence of a secondary RLS; (2) the presence of pathologies frequently associated with RLS that do not respond to any dopaminergic treatment or bear any risk for this type of therapy; (3) RLS symptoms occurring in the context of drug withdrawal; and (4) the concomitant use of drugs likely to influence sleep architecture or motor manifestations during sleep. Inclusion was possible if these drugs were sufficiently washed out (at least 5 half-lives) prior to entry into the study, if medically acceptable	Severe to very severe	302 (248) / 61 ± 11 / 80 M: 222 F (73% F)	In 48% of the study participants, investigators reported adverse events suspected to be drug related. Most adverse events were mild and transient and related to the gastrointestinal system (nausea: 16.6%) or the central nervous system (dizziness: 7.0%, headache: 4.6%). Premature dropout from the study occurred in 54 patients (17.9%), in 17 patients (3.0%) due to a drug related adverse event.	RLS-6 and the International RLS Rating Scales The severity of RLS symptoms at night, at bedtime, and during the day, as well as the IRLSRS total score improved during therapy. Satisfaction with sleep was increased (all P values < .001). In 5% of all patients, RLS symptoms worsened, and in a further 6.3%, response to therapy was poor. In 9 patients (3.0%) between 1 and 3 criteria for augmentation were noted. The median change in severity between baseline and final assessment was a symptom reduction of -69.8%; almost every fourth patient (23.3%) of the total sample was free from symptoms at study end according to the total score of the IRLS. In total, 205 patients (68.1%) experienced a > 50% reduction in RLS symptoms compared to 15 patients (5.0) who showed no improvement at the end of the individual study. IRLSRS baseline = 26.8 ±5.9; Endpoint = 9.7 ±9.0	Long-term therapy with cabergoline is a safe and well-tolerated treatment option for the great majority of patients with idiopathic RLS. The treatment was efficacious both for nighttime and daytime symptoms in this indication and may carry a low risk of augmentation.	
Benes, 2006 (116) ORAL	Patients aged 25 to 75 years were eligible to participate. Two groups of patients were selected, de novo RLS patients (i.e. newly diagnosed and without a history of dopaminergic treatment, "NOV" study) as well as advanced RLS patients pretreated with levodopa ("LEV" study). In the PSG at baseline, patients must show a PLMS arousal index >5=/h as well as either sleep latency of more than 25 minutes or sleep efficiency of less than 85% or both. Patients of the NOV study must not be pre-treated with any dopaminergic therapy whereas patients of the LEV study must have a stable previous levodopa therapy, however, without sufficient control of their RLS symptoms.	Moderate or severe included; title indicates "advanced disease"	NOV: 10 / 54 ± 11 (34–75) / 1 M 9 F LEV: 10 / 66 ± 7 (56–75) / 4 M 6 F	No serious adverse events occurred throughout the study. In one patient of the NOV study, lisuride treatment (0.4 mg=day) was discontinued after three weeks due to dizziness and nausea. Eight adverse events were reported in five patients of the NOV study and two adverse events in two patients of the LEV study. The adverse events were typical for dopaminergic drugs: nausea (three patients), fatigue (two patients, one in the LEV study), vomiting, gastric pain, hypotension, dizziness, and increased anxiety (LEV study) in one patient each. With the exception of nausea and dizziness in one patient, none of the adverse events was rated as severe.	Prior to baseline, the patients were assessed by polysomnography (PSG) for two nights (one adaptation night, one assessment night) and after seven days of treatment. A final assessment using Clinical Global Impressions (CGI) was performed after four weeks. Marked improvements occurred in both studies in different PLM indexes and in the CGI. Levodopa dose could be decreased by 27%. In the LEV study, the average levodopa dose (decarboxylase inhibitor not considered) at pre-treatment was 205± 68.5mg=day (range 100 to 300 mg); the dose decreased by 55 ±68.5 mg=day (=27% of baseline dose) until the end of the study. One patient could be withdrawn from levodopa completely (at a lisuride dose of 0.4 mg). The maximum dose of levodopa at study end was 200mg/day in the LEV study.	Lisuride might be an efficacious treatment for RLS in general, and in combination with levodopa in advanced stage. The findings of our two proof-ofprinciple studies indicate that oral lisuride is well tolerated and effective as monotherapy for de novo RLS patients and in combination with levodopa for those RLS patients with insufficient levodopa effects.	
Benes, 2006 (115) PATCH	Severe and long-lasting idiopathic RLS. Inclusion: Patients aged 18–75 years with a minimum score of 10 (range 0='no symptoms' to 40='very severe' intensity) on the IRLS severity scale (at least 'moderate RLS'), a minimum score of 3 in the RLS-6 scale indicating 'severity of RLS during the day when at rest' (range 0='no symptoms' to 10='very severe' intensity), and had responded previously to levodopa if pre-treated. Patients were excluded for the following reasons: any form of secondary RLS, history of sleep disturbances if not caused by RLS, concomitant neurological or central nervous diseases, or psychotic episodes. Concomitant therapy with neuroleptics, hypnotics, antidepressants, anxiolytic drugs,anticonvulsive therapy, psychostimulatory drugs, L-dopa, dopamine agonists or opioids was excluded and must have been washed out for a sufficient period of time (at least 3 days or at least five half-lives if longer) at baseline.	A minimum score of 10 on IRLS; Actual was "severe"	Exception to exclusion criteria for Part 2 Part 1: 13 (10) / 58± 6 / 9F 4M Part 2: 10 (9) / 58± 4 / 6F 4M	No serious adverse events occurred during the study. None of the patients were pre-maturely withdrawn from the study due to safety problems. A total of 12 adverse events were recorded in five patients; of those, 10 events in four patients were considered drug-related. The drug-related adverse events were typical for dopaminergic drugs (nausea (three patients), vomiting, gastroenteritis, headache, fatigue, hyperhidrosis in one patient each) or transdermal systems (skin reactions in two patients). One patient with nausea and vomiting had to receive the peripheral dopamine antagonist domperidone (20 mg p.o., three times per day). None of the adverse events were rated as severe.	IRLSSG rating scale total score as primary efficacy measure and the RLS-6 scales (severity at bedtime, during the night, during the day when the patients were at rest or active, quality of sleep, daytime tiredness) . As an objective test, an actimetry method validated for periodic leg movements in RLS patients (MOVOPORT) was applied for six 3-day periods prior to and after baseline, at week 2 (end of open-label period), and at week 3 (end of double-blind period). The Epworth Sleepiness Scale (ESS)was used to investigate daytime sedation. Severity of RLS clearly improved during open-label and double-blind treatment with lisuride but became worse under placebo according to the International Restless Legs Syndrome Study Group Rating Scale (IRLS), RLS-6, and Clinical Global Impressions (CGIs) scales, and actigraphy assessments (periodic leg movement index) in the 1-week double-blind period. IRLS baseline (32.4±5.9), after 2 weeks lisuride (-22.1±11.6), after randomization (change from 2-week lisuride): lisuride change (-1.4±5.9) and placebo (+11.5±10.9)	The explorative findings of this small controlled study suggest that lisuride patches might be an efficacious treatment for RLS patients without clinically relevant tolerability problems.	With one exception, all patients were pre-treated with dopaminergics and six patients had experienced augmentation due to previous levodopa therapy.
Bliwise, 2005 (52)	Only patients with primary RLS were included; patients with secondary RLS due to other conditions, such as diabetes or peripheral neuropathy, were excluded as were women of child-bearing potential who were not using birth control. Patients with Parkinson's disease, sleep apnea, untreated depression and any systemic disease including hepatic, renal, or endocrine disorders were excluded. Additionally, we excluded patients with recent or current evidence of alcoholism or drug dependency or individuals ingesting over three caffeinated beverages per day.	Not stated	33 (22) / 50.8 / 50.8 (46.4–55.2) / 9M 13F	Side effects were typical of all dopamine agonists and were dose related. The majority of patients elected to continue treatment with ropinirole upon study completion. Nausea was the most common side effect (n=17, 65%), occurring with a mean titrated ropinirole dose of 0.82 (SD=1.05) mg. The next most common side effects were daytime somnolence (n=11, 42%) at a mean titrated dose of .66 mg (SD=0.80) and headache (n=6, 27%) at a mean titrated dose of .46 mg (SD=0.19). Other less commonly reported symptoms during the open-label phase were dizziness (n=2, 8%) and skin changes (n=1, 4%). Analyses of possible treatment-emergent side effects occurring subsequent to the randomization showed no significant differences between rates of side effects for the two groups at visit 6 or visit 7.	Assessment of periodic leg movements in sleep (PLMS) recorded with nocturnal polysomnography and RLS symptoms as assessed with the IRLSSG Rating Scale. Secondary outcomes included sleep macroarchitecture. Ropinirole significantly decreased PLMS. Ropinirole signficantly decreased RLS symptoms only during open-label portion of trial (22.6±4.6 to 8.7±8); at the end of 2-week double blind trial, ropinirole not differ from placebo in IRLSRS. Sleep macroarchitecture did not change. PLMs increased from 19.2±15 to 76.4±40 on placebo and kept constant at 19.7±20 to 19.8±20 on ropinirole.	Ropinirole successfully treated long-standing RLS and can be considered a viable short-term treatment for this condition.	

Evidence Table
The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Inclusion/ Exclusion criteria	RLS Severity	Sample size (completed) / mean age (age range or standard deviation) / gender of subjects	Adverse effects	Outcome measures / results	Conclusions	Comments
Bogan, 2006 (49) **TREAT RLS US Study**	Men and women 18-79 years with primary RLS. Inclusions: a baseline IRLS total score of ≥15, a history of ≥ 15 nights of RLS symptoms during the previous month, and RLS symptoms for at least 4/7 nights during the screening / washout phase. Exclusions: signs of secondary RLS, including renal failure, pregnancy, and iron deficiency anemia; experience of augmentation or rebound with previous treatment or daytime symptoms; taking medication known to affect RLS or sleep or if they had undergone withdrawal, introduction, or change in dose of any drug known to substantially inhibit or induce cytochrome P-450 1A2; a known intolerance to ropinirole or any other dopamine agonist and those with a history of alcohol or drug abuse within 6 months of screening; other primary sleep disorders (eg, narcolepsy, clinically important parasomnias, or sleep-disordered breathing), movement disorders (eg, Parkinson disease, dyskinesias, or dystonias), or medical conditions that could affect the assessment of RLS (eg, diabetes, fibromyalgia, peripheral neuropathy, or rheumatoid arthritis).	Moderate to severe (IRLS≥15)	392 (331) / Ropinirole: 52.2 (12.79) Range 18-79; Placebo 52.4 (13.15) Range 19-78 / Ropinirole 109F 78M; Placebo 123F 70M	Ropinirole was generally well tolerated, with an adverse-event profile consistent with other dopamine agonists. Overall, 82.9% of patients (155/187) in the ropinirole group and 66.8% of patients (129/193) in the placebo group reported at least 1 AE during the treatment phase of the study. The most common (reported by at least 5% of patients) AEs are nausea, headache, somnolence, nasopharyngitis, dizziness, and vomiting. With the exception of headache and nasopharyngitis, all these events were reported reported by a greater proportion of ropinirole-treated patients compared with placebo-treated patients. Three patients in the ropinirole group (1.6%) and 1 in the placebo group (0.5%) had reports with the term augmentation noted. These events occurred during the treatment phase of the study.	The primary end point was mean change from baseline to week 12 in IRLS total score.Significant treatment differences favoring ropinirole, compared with placebo, were observed for change in IRLS total score at week 12 (adjusted mean treatment difference, –3.7; 95% CI, –5.4 to –2.0;P<.001) and for all 3 key secondary end points: mean change from baseline in IRLS total score at week 1 and proportion of patients who were much/very much improved on the CGII scale at weeks 1 and 12. Ropinirole was associated with significantly greater improvements in subjective measures of sleep disturbance, quantity, and adequacy; quality of life; and anxiety. Although treatment differences favoring ropinirole in daytime somnolence were observed, they were not statistically significant (P=.10). Significantly more patients in the ropinirole group (137/ 187 [73.3%]) were rated as responders on the CGI-I scale at week 12 LOCF compared with those receiving placebo (109/193 [56.5%]; adjusted odds ratio, 2.1; 95% CI, 1.4- 3.3; P<.001). The mean (SD) PLM index decreased from 39.8 (27.55) at baseline to 15.6 (22.55) at week 6 observed case in the ropinirole group and from 32.8 (22.25) to 27.5 (20.09) in the placebo group. This change in PLM index was significantly different favoring ropinirole; the adjusted mean treatment difference was –14.5 (95% CI, –20.3 to –8.7; P<.001).	This study confirms that ropinirole improves RLS symptoms and subjective measures of sleep, quality of life, and anxiety and that it is generally well tolerated.	
Bogan, 2010 (89)	Men and women, at least 18 years of age, diagnosed as having moderate to severe primary RLS (International RLS Study Group criteria)' were recruited. Eligible patients had RLS symptoms on at least 15 nights during the month before screening (or, if undergoing treatment, similar symptom frequency before treatment initiation), symptoms on at least 4 nights during the 7-day screening period, an IRLS total score of at least 15 points at the beginning and end of the baseline period, and creatinine clearance of at least 60 mL/min. If patients were receiving treatment for RLS or a sleep disorder, use of medication was to be discontinued at least 2 weeks before baseline. Patients were excluded if they were pregnant or breastfeeding; had evidence of secondary RLS; had a body mass index (calculated as weight in kilograms divided by height in meters squared) of more than 34; were currently experiencing a moderate or severe major depressive disorder (DSM IV R)had primary sleep disorders, neurologic disease, or movement disorders other than RLS; or had a history of RLS symptom augmentation or end-of-dose rebound with previous RLS treatment. Although the presence of daytime (10 AM to 6 PM) RLS symptoms for at least 2 days during the week before baseline was originally an exclusion criterion, this restriction was removed after enrollment of approximately 10% of the total study population.	IRLS ≥ 15; actual patient average in the severe range	SB: 327 (221) DB: 194 (84)/ SB 19-82 (50.3) DB placebo 23-82 (52.2) Gabapentin encarbil 19-73 (50.7)/SB 179F 132M DB 114F 79M	SB:Treatment-emergent AEs were reported by 264 (81.0%) of 326 patients, most of which were mild or moderate in intensity (Table 3). Of 326 patients, 42 (12.9%) reported at least 1 AE that led to withdrawal; in 32 of these patients, investigators considered these AEs to be treatment related. Adverse events that led to the withdrawal of more than 1 patient were somnolence (n=6), dizziness (n=5), headache (n=5), constipation (n=3), fatigue (n=3), insomnia (n=3), blurred vision (n=2), decreased libido (n=2), diarrhea (n=2), feeling abnormal (n=2), and nausea (n=2). Adverse events that led to withdrawal in one patient each are presented in the footnote of Table 3. DB:Treatment-emergent AEs were reported by 49 (51%) of 96 gabapentin enacarbil-treated patients and 45 (46%) of 98 placebo-treated patients. Most AEs were mild or moderate in intensity (Table 3). There were no reports of severe somnolence or dizziness.	Almost 60% of patients in this study met response criteria after 6 months of SB treatment with gabapentin enacarbil, 1200 mg, reporting sustained improvements in IRLS total score and investigator-rated impressions of global improvement. However, patients who did not complete the 24-week SB phase were not eligible to be considered responders. After DB randomization, patients who continued receiving gabapentin enacarbil, 1200 mg, demonstrated significantly lower rates of RLS symptom relapse after 36 weeks of treatment compared with those who received placebo. The time to onset of RLS symptoms was also significantly delayed in gabapentin enacarbil-treated patients during a 24-hour assessment period at the end of treatment. In addition to relapse rates, measures of RLS symptoms (eg, IRLS total scores, investigator- and patient-rated CGI-I ratings, MOS Sleep Scale scores, and PSQ outcomes) indicated that placebo-treated patients had significantly more RLS symptoms than gabapentin enacarbil-treated patients during the DB phase.	Gabapentin enacarbil, 1200 mg, maintained improvements in RLS symptoms compared with piacebo and showed long-term tolerability in adults with moderate to severe primary RLS for up to 9 months of treatment.	
Braun, 2009 (114) **plus domperidone (In Background section)**	Male Caucasian subjects between 18 and 45 years of age with a body mass index (BMI) between 20 and 28 kgm-2 were included in the study. They had to be in good health, with no clinically relevant medical or psychiatric abnormalities. Known or suspected hypersensitivity, in particular to the study medication, a history of atopic eczema and/or an active skin disease, and any concomitant medication within 2 weeks prior to first dosing led to exclusion.	No RLS (healthy)	16 / 30.3 ± 7.8 years (range 21-44) / 16M	No serious AE occurred during the study; all 41 reported treatment-emergent AEs were of mild or moderate intensity. Of these,46% were reported during co-administration with domperidone compared with 54% experienced without domperidone treatment. The most common AEs were reddening and pruritus at the patch application site in both treatment periods. A difference between treatments was observed for the number of subjects experiencing nausea, which was lower during domperidone comedication (one subject with nausea episode vs. four subjects with nausea in the treatment period without domperidone).Vomiting only occurred once in each treatment group.	Pharmacokinetic variables describing systemic exposure and renal elimination of rotigotine and metabolites, and safety and tolerability of the treatment were assessed. The primary steady-state pharmacokinetic parameters ($C_{max,ss}$ and $AUC_{(0-24),ss}$) were similar with or without co-administration of domperidone. Geometric mean ratios were close to 1 and respective 90% confidence intervals were within the acceptance range of bioequivalence (0.8, 1.25): $C_{max,ss}$ 0.96 (0.86, 1.08) and $AUC_{(0-24),ss}$ 0.97 (0.87, 1.08). $t_{max,ss}$, $t_{1/2}$, secondary parameters calculated on days 4/5 after repeated patch application ($C_{min,ss}$, $C_{ave,ss}$, $AUC_{(0-tau)}$) and renal elimination for unconjugated rotigotine and its metabolites were also similar with and without comedication of domperidone. A reduction in the dopaminergic side-effect nausea was seen with domperidone comedication.	No changes of pharmacokinetic parameters describing systemic exposure and renal elimination of rotigotine were observed when domperidone was administered concomitantly with rotigotine. The lack of pharmacokinetic interactions indicates that a dose adjustment of rotigotine transdermal patch is not necessary with concomitant use of domperidone.	
Cuellar, 2009 (124)	Inclusion: At least 21, not satisfied with current treatment outcomes, have symptoms of RLS 3 nights/week or more. Exclusion: Positive toxicology report, liver function profile abnormal, and 3 yes answers on CAGE 2. Participation in a clinical study with an investigation drug within 3 months; Current use of vitamins or minerals beyond the recommended RDA requirements; Current use of any herbs or natural products; Current use of benzodiazepines or barbiturates; Another sleep disorder other than RLS; Use of valerian within 120 days of baseline visit; History of liver disease including cirrhosis, alcoholism, and hepatitis; Pregnant, nursing, or intending to become pregnant in 3 months	23.6 ± 7.0 (moderate to very severe)	48 (37) / 49.5 ± 13.1 (36-65) / 27F10M	There were 8 withdrawals, only 3 of which were from the experimental group. Reasons for the withdrawals related to the valerian were rash, RLS symptoms worsening, and stomach irritation.Reported adverse events were: GI disturbances (4), fatigue/mental sluggishness (4), vivid dreams (1), agitation/restlessness (2), headache (1), dizziness (1), and rash (1).	The primary outcome of sleep was sleep quality (latency) (PSQI) with secondary outcomes including sleepiness (ESS) and RLS symptom severity (IRLSSS). Both groups reported improvement in RLS symptom severity and sleep. In a nested analysis comparing sleepy vs nonsleepy participants who received 800 mg of valerian (n=17), significant differences before and after treatment were found in sleepiness (P=.01) and RLS symptoms (P=.02). A strong positive association between changes in sleepiness and RLS symptom severity was found (P=.006). ESS: Placebo baseline 10.4 ± 6.1 (SD); change 2.8 ± 3.7 Valerian baseline 11.7 ± 5.4; change 3.4 ± 4.4, pvns between placebo and valerian PSQI Global: Placebo baseline 12.4 ± 5.0; change 4.4 ± 4.8 Valerian baseline 14.4 ± 3.7; change 4.5 ± 5.3 RLSSS: Placebo baseline 24.0 ± 8.0; change 4.7 ± 10.4 Valerian baseline 23.0 ± 5.9; change 3.4 ± 9.4	The use of 800 mg of valerian for 8 weeks improves symptoms of RLS and decreases daytime sleepiness in patients that report an ESS score of 10 or greater. Valerian may be an alternative treatment for the symptom management of RLS with positive health outcomes and improved quality of life. Because we did not use any objective measures in this study, the placebo effect may explain why we did not find differences between the treatment and placebo groups. Thus, an important result of the pilot study was appreciation of the magnitude of the placebo effect. The placebo effect has been reported to be considerably less significant when measuring PLMS. Consistently, we find that valerian is a safe herb with minimal adverse events and suggest higher doses could be used in research studies.	Most subjects had severe (38.9%) or very severe (19.4%) RLS symptom severity scores on admission to the study
Davis, 2000 (99)	To be included in the study, patients had to have symptomatic RLS and be under treatment at the time of enrollment. Exclusion criteria included allergy to iron sulfate, anemia (hemoglobin <10), current or recent treatment with iron sulfate (200 mg or more per day for at least half of the days in the past 6 months), current pregnancy, hemochromatosis, peptic ulcer disease, history of gastrointestinal neoplasm within the past 2 years, active bacterial infection, or current treatment with medications known by the patients to exacerbate their RLS. Patients were included regardless of other potential causes of RLS, such as neuropathy, renal disease, etc.	Not described by uniform IRLS criteria	125 eligible / 36 responded to invitation / 28 enrolled (24 completed) / Iron: 58.6 (33-80) Placebo: 59.9 (33-76) / Iron: 5M9F Placebo: 4M10F	Adverse events were recorded in a total of 9 patients. They included nausea and/or constipation (n = 5), darkcolored stools (n = 3), tooth discoloration (n = 2), vertebral fracture (n = 1), worsening of RLS symptoms (n = 1), and bladder spasms (n = 1). Some patients had more than one adverse event. All of the adverse events were seen in patients taking iron sulfate.	The primary outcome measure was the dichotomous variable of improvement or no improvement in average quality of sleep as recorded by a visual analog scale nightly over a 2-week period, comparing a pretreatment 2-week baseline to weeks 13–14. Secondary outcome measures included a comparison of the quality of sleep as measured by a visual analog scale, effect of restless legs syndrome on life as a whole as measured by a different visual analog scale, and the percentage of nights patients were symptomatic.	No significant differences were noted between iron and placebo groups for both primary and secondary outcome measures. Responders taking iron did have a significant increase in their iron saturation saturation compared to nonresponders taking iron. Conclusions: Iron sulfate does not appear to be an effective empiric treatment for restless legs syndrome.	In addition, iron therapy resulted in numerous adverse events that were not seen with placebo. Based on these results, it appears that iron sulfate is not an effective adjunctive treatment for RLS. This trial also suggests that iron monotherapy may not be an adequate treatment for RLS. Overall, patients who took iron did not show a significant increase in iron parameters. However, those who reported improvement did have a statistically significant increase in their iron saturation compared to those who did not improve. The reasons for lack of improvement in iron status in those patients taking iron are unclear.
Earley, 2004 (103)	Inclusion criteria included: all four basic features required for the diagnosis of RLS, no secondary causes for RLS, and periodic leg movements in sleep (PLMS) greater then 20 per hour. Exclusion criteria included: anemia, ferritin .300 mcg/l, percent iron saturation .45%, clinically significant sleep disruption for reasons other then RLS, pain-related conditions that would confound the interpretation of RLS symptoms, active cardiac problems, or conditions excluding MRI assessment.	Half had a symptom severity score (JHRLSS scale) of 2 (moderate severity with symptoms usually starting in the evening) and the other half had a score of 3 (severe, with symptoms usually starting during the daytime before 6 pm).	11 (10) /51-74 (62.4) /6M 4F	The data for one subject, who reported feeling short of breath after 30 mg of iron had been infused, were excluded from the analysis; the infusion was stopped and the subject was treated for possible acute allergic reaction. No other major side effects were seen with the iron infusion	The mean ±SD of percent decrease after treatment was 54 ± 41% for GRS scores (P< 0.002); 28 ± 32% for PLMS/h (p= 0.01); 57±37% for hours per day with RLS (P< 0.001) and the percent increase in TST was 18 ± 25% (P= 0.025). Despite the overall mean improvements in symptoms, 4 out of the 10 subjects were classified as Non-Responders.	The results in this study provide valuable information for future studies, but the efficacy and safety of IV iron treatment for RLS remain to be established in double-blind studies. The serum ferritin results suggest that greater than expected iron loss occurs after IV iron loading.	

Evidence Table
The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Inclusion/ Exclusion criteria	RLS Severity	Sample size (completed) / mean age (age range or standard deviation) / gender of subjects	Adverse effects	Outcome measures / results	Conclusions	Comments
Earley, 2009 (101)	Exclusion criteria included: possible secondary forms of RLS; hemoglobin <12 g/dl; any pain-related conditions or any other sleep-related problems that might interfere with the interpretation of the outcome measures; sleep apnea rates >25/h; any organ problems (by history or blood study), that would affect RLS symptoms or the treatment with iron. Patients were required to have periodic leg movements of sleep (PLMS), >15/h on the second-night polysomnogram, which was performed during their stay in the General Clinical Research Center (GCRC).	Severe to very severe	At the time of the interim analysis there were 7 placebo and 11 iron-treated subjects / Patients in their 60s on average / 55% Treatment and 71% placebo were F	The commonest reported side effects from treatment (see Table 3) were edema in either hands or feet (36%) and nausea or vomiting (36%). Hypotension (18%), dizziness (18%) and abdominal pain (9%) were also reported with treatment. All of the reported side effects occurred during treatment and resolved within minutes to hours of completing the infusion. No adverse effects were reported at two-week follow up after the iron treatment.	Primary measures of the clinical status were global rating scale (GRS) and periodic leg movements of sleep (PLMS). Primary measures of brain iron status were CSF ferritin and MRI-determined iron in the substantia nigra. At 2-weeks post-treatment, iron treatment resulted in a small but significant increase in CSF ferritin and a decrease in RLS severity (GRS) but did not change PLMS or MRI iron index. None of the secondary outcomes changed with treatment. There was no single case of clear treatment benefit in any of the patients.	High-dose IV iron failed to demonstrate the robust changes reported in three prior open-label studies. Differences in iron formulation, dosing regiment, and peripheral iron status may explain some of the discrepancies between this and previous IV iron treatment studies.	This interim analysis revealed an effect size that was too small to allow for adequate power to find significant differences with the planed 36-subject enrollment for either the primary objective outcome of PLMS or any of the secondary outcomes. The study was stopped at this planned break-point given the lack of both adequate power and any indication for clinically significant benefit.
Ehrenberg, 2000 (153)	PLMD. If the sleep history suggested the presence of a sleep disorder and there were subjective complaints such as fatigue or daytime somnolence, a polysomnogram (PSG) was obtained.	N/A	6 (five women, one man; mean age, 41.5 years; range, 28-62 years)	One patient discontinued VPA 1 month after completion of the last PSG because of short-term side effects, and one patient stopped VPA 22 months after the last PSG because of weight gain.	All six patients experienced subjective improvement in daytime alertness. Sleep efficiency was improved from 76% to 88% (p = 0.003), stage 1 (light) sleep decreased from 26% to 13% (p = 0.04), stage 3 and 4 (deep) sleep increased from 19% to 30% (p = 0.01), and rapid eye movement sleep was unchanged. There was a trend toward a reduction in the number of PLMs per hour of sleep and in the percentage of arousals associated with PLMs. All of the patients continued taking VPA after the PSGs were completed.	Thus, these data indicate that VPA has a long-term beneficial effect on sleep consolidation in patients with PLMD.	
Eisensehr, 2004 (123)	Idiopathic RLS. Patients were included if they had a PLMS index (PLMI) of>10/h of total sleep time (TST) and had suffered from RLS daily for at least six months prior to the study. Patients with signs of any other sleep disorder or severe additional disease and polyneuropathy, pregnant or lactating women and women without safe contraception were excluded. Patients taking any medication suggested as treatment for RLS had to stop this medication five days prior to study entry. Any other medication had to be stable throughout the study.	Moderate-to-severe idiopathic RLS	20 / age: 58.9±6.9 years (range: 41–74) / 12F 8 M	There were similar side effects between the three groups and nine patients reported side effects with placebo therapy. That indicates successful blinding at least partially. Nine of the 20 patients suffered from side effects with VPA, 9 with placebo and 13 with LD therapy (NS). Side effects are summarized in article.	PSG and a VAS rating scale at the end of each 3-week treatment periods. There was no major difference between the efficacy of valproic acid or LD. Periodic leg movements in sleep (PLMS) and PLM arousal index (PLMAI) significantly decreased with LD ($p \leq 0.005$). However, LD, but not VPA, significantly increased arousals not associated with PLMS (p=0.002). Decrease of intensity and duration of RLS symptoms were more pronounced with VPA ($p \leq 0.022$) than with LD (NS) Follow up 6 to 18 months after the study end was achieved in 19 patients and revealedthat VPA was still effective in 75 % (9 out of 12 patients) whereas only 29 % (2 out of 7 patients) were still satisfied with LD (p=0.048).	We conclude that slow-release VPA provides a treatment alternative for RLS. Therefore,we do not recommend VPA as a first-line treatment for RLS. However, VPA may be an effective alternative or adjunctive treatment for patients unable to tolerate dopaminergics, or suffering from augmentation.	
Ellenbogan, 2011 (88)	Patients included from 1 of 4 parent studies and had received blinded treatment of gabapentin enacarbil or placebo for up to 12 weeks.The study was conducted at 67 centers in the US between 2006 and 2008	Moderate to severe	A total of 581 (77.4%) of 751 eligible subjects who completed one of the 4 parent studies were enrolled, and 573 were included in the safety population; 197 subjects were gabapentin enacarbil-naive, and 376 were non-naive (Fig. 2). Overall, 386 (66.4%) of 581 subjects completed the study; withdrawal rates were higher in the gabapentin enacarbilYnaive subgroup (35.7%) compared with the non-naive subgroup (30.4%) The mean age of subjects was 50.2 years (range, 19±79 years). More than half of the subjects were women (58.6%), and 96.3% were white.	Safety assessments included the incidence and severity of treatment-emergent adverse events (AEs), serious AEs (SAEs), and AEs leading to withdrawal. Other safety assessments included vital signs, clinical laboratory tests, and electrocardiograms (ECGs). Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS),12,13 where ESS scores higher than 10 were considered to represent excessive daytime sleepiness. A Sudden Onset of Sleep (SOS) Questionnaire was used; Presence of reemergence/rebound of RLS symptoms was examined using a subject-rated 24-hour RLS diary.	Efficacy assessments included mean change from parent study baseline in International Restless Legs Scale (IRLS) total score and the proportion of subjects rated as responders (''much improved'' or ''very much improved'') on the investigator-rated Clinical Global ImpressionYImprovement (CGI-I) scale at week 52 (last observation carried forward [LOCF]). The definition of baseline differed by variable. Parent study baseline assessments were used for the IRLS total score and investigator-rated CGI-I scale. Week 0 assessments from the present study were the baseline values for all safety assessments, collected at the visit in the parent study in which the final efficacy or safety assessment was conducted. The safety population comprised 573 subjects; 386 (67.4%) completed the study. Treatment-emergent AEs were reported by 80.1% of subjects and led to withdrawal in 10.3% of subjects; most (67.7%) were mild or moderate in intensity. The most common AEs were somnolence and dizziness (19.7% and 11.5% of subjects). Twenty subjects (3.5%) reported serious AEs; one subject died (fall, 25 days after stopping gabapentin enacarbil, judged not treatment related). No serious AE occurred in more than 1 subject. No clinically relevant changes were reported in vital signs, laboratory parameters, or electrocardiograms. At week 52 last observation carried forward, the mean (SD) change from parent study baseline in International Restless Legs Scale total score was Y15.2 (8.85 [parent study baseline score, 23.2 (5.03)]), and 84.8% of subjects were Clinical Global ImpressionYImprovement responders (''much improved'' or ''very much improved'').	Gabapentin enacarbil was generally safe and well tolerated and improved RLS symptoms in subjects with moderate-to-severe primary RLS for up to 64 weeks of treatment.	
Ferini-Strambi, 2008 (30)	Adults with moderate or severe RLS. Men and women (18–80 years old) with RLS were enrolled at 49 outpatient centers in Europe. Patients were required to have RLS symptoms at least 2–3 times per week in the 3 months before study entry and a score >15 on the International RLS Study Group Rating Scale (IRLS) at baseline. Patients were excluded for medical disorders that might compromise the evaluation of study results or increase a patient's health risks. These disorders included but were not limited to clinically significant renal or hepatic disease, insulin-dependent diabetes, clinically significant laboratory abnormalities, and any history or presence of non-RLS sleep disorders, major depression, psychotic disorders, suicidal behavior/ideation, or malignant melanoma. Women of childbearing potential were required to practice adequate contraception, and pregnant or lactating women were excluded.	Moderate or severe	357 (278) / Placebo: 56.9 (13.0) Pramipexole: 56.3 (12.4) / Placebo: 119F, 68M; Pramipexole 132F, 50M	Nine percent of patients in each group withdrew because of adverse events. Over the course of the 12-week trial, 106/182 (58.2%) patients of the pramipexole group and 86/187 (46.0%) of the placebo group reported at least 1 AE. Most AEs were mild or moderate in severity (52.2% for pramipexole, 40.6% for placebo). There were 6 serious AEs reported, 4 in the pramipexole group (second degree atrioventricular block, disc protrusion, sciatica, and syncope) and 2 in the placebo group (fatal myocardial infarction and upper abdominal pain). The most common AE was headache reported by 14.8% of the pramipexole group and 12.8% of the placebo group, followed by nausea (17.6% vs. 5.9%), nasopharyngitis (7.1% vs. 4.8%), and fatigue (8.8% vs. 2.1%). Overall, the trial's safety findings were consistent with the known safety profile of pramipexole.	The co-primary outcome measures were change in Medical Outcomes Study (MOS) sleep disturbance (initiation and maintenance) score and International RLS Study Group Rating Scale (IRLS) score at 12 weeks. At 12 weeks, the adjusted mean change from baseline was greater for pramipexole (vs. placebo) for IRLS score (-13.4 ± 0.7 vs. -9.6 ± 0.7) and MOS sleep disturbance score (-25.3 ± 1.5 vs. -16.8 ± 1.5) ($p \leq 0.0001$; ANCOVA). Responder rates (clinical and patient global impression and IRLS) were also significantly higher in the pramipexole group. RLS-QOL score was improved over placebo at Week 12 ($p < 0.01$) as were MOS sleep adequacy ($p = 0.0008$) and quantity ($p = 0.08$) scores.	Pramipexole is effective and well-tolerated for RLS and related sleep disturbance.	
Garcia-Borreguero, 2002 (91)	Patients with a ferritin value below 45 mcg/mL were included and classified as iron deficient. Patients with ferritin levels below 20 mcg/mL were excluded.	Not stated, but data indicates moderate	24; 22 idiopathic and 2 secondary to iron deficiency (22) / 55±11.6 yrs (33-75) / 8M16F	Nearly 48% of patients taking gabapentin and 20.8% of patients taking placebo ($p<0.05$) reported adverse effects. Commonly reported adverse effects were malaise, abdominal pain, somnolence, headache, and dyspepsia. No significant differences were found in the particular rate of any of these adverse effects between gabapentin and placebo. Moreover, none of these adverse effects led to a discontinuation of treatment.	Patients were rated at baseline and at scheduled intervals by the RLS Rating Scale, CGIC, PGIC, pain analogue scale, PSQI, PSG Compared to placebo, gabapentin was associated with reduced symptoms on all rating scales. Sleep studies showed a significantly reduced PLMS index (11.3±3.3 SD=15.5 vs. 20.8±3.3; p=0.05) and improved sleep architecture. Patients whose symptoms included pain benefited most from gabapentin. RLS rating scale after 6 weeks was 9.5±1.3 (SE) [6.1 SD] for gabapentin vs. 17.9±1.3 [6.1 SD] for placebo; p<0.0005 vs. baseline of 20 (SE and SD not given).	Gabapentin improves sensory and motor symptoms in RLS and also improves sleep architecture and PLMS,	No patient experienced augmentation
Garcia-Borreguero, 2007 (56)	Eligible patients from four parent studies [Study 188 (36-week maintenance-of-effect study), Study 190 (TREAT RLS 1; 12-week efficacy study), Study 194 (TREAT RLS 2; 12-week efficacy study [non-US subjects only]) and Study 218 (7-week pharmacokinetic study), were invited to participate. At parent study entry, all patients had a score of ≥15 on the IRLS. Patients suffering from RLS symptoms requiring daytime treatment (daytime defined as 10:00 until 18:00 h) were excluded from the parent studies. Patients were excluded from the present study if they had clinically significant abnormal laboratory or electrocardiographic (ECG) findings that were not resolved prior to screening. Women of childbearing age who were not practising a clinically accepted method of contraception or who had a positive pregnancy test were also excluded, as were any subjects who had developed any medically unstable illness.	≥15 on the International Restless Legs Scale (IRLS) [at least mid-moderate]	310 (251; 309 in safety population) / 56.5 (11.04) Range 25-80 in safety population / 186F 123M	282 patients (91.3%) reported at least one on-treatment AE. The incidence was higher in those newly exposed to ropinirole compared with those who had received the drug previously in the parent study (96.0% versus 88.1%). The majority of those patients reported AEs that were mild or moderate in intensity: 224 (72.5%) reported a mild AE, 213 (68.9%) reported a moderate AE, and 102 (33.0%) reported a severe AE. The most commonly reported AE (P10%) was nausea (37.2%; Table 2). About two-thirds of patients reporting this event reported a single episode (74/115, 64.3%). Of the 115 patients reporting nausea, the majority (85.2%) reported nausea that was mild or moderate in intensity.	The primary study objective was to evaluate the safety of ropinirole. Efficacy was assessed by change in IRLS score, as well as by global improvements (clinical global impression [CGI] scale) and improvements in measures of sleep, work productivity, and quality of life. Results: A total of 282 patients (91.3%) reported ≥1 adverse event. For the majority of patients, the reported adverse events were mild or moderate in intensity. The most common adverse event was nausea. Adverse events led to discontinuation in 8.7% of patients. At week 52, IRLS scores improved by an average of 12.0 points from baseline, and 82.8% of patients were 'much improved' or 'very much improved' on the CGI-improvement scale. Ropinirole treatment was also associated with improvements in measures of sleep and quality of life.	Ropinirole was well tolerated and therapeutic efficacy was maintained over 52 weeks in patients with RLS.	
Garcia-Borreguero, 2010 (93)	Men and women aged 18–80 years with idiopathic RLS total score ≥15 points at baseline) that interfered with sleep onset or sleep maintenance on 4 nights/week for at least 6 months were included in the study. Exclusion criteria were any form of secondary RLS, coexistence of severe medical or psychiatric disorders, previous treatment lasting > 12 weeks with DAs, serum ferritin 10 < g/L, severe comorbid sleep disorders that might confound assessment, or shift work also PLMS<10/hr.	Moderate to severe	58 (43) / 48 for pregabalin and 53 for placebo / 59 % female	Pregabalin was generally well-tolerated. Adverse events were mild but common, and included unsteadiness, daytime sleepiness, and headache.	Endpoints were mean change from baseline in the International Restless Legs Scale (IRLS) total score, Clinical Global Impression (CGI), and RLS-6 scales, as well as changes in periodic limb movements (PLMs) and sleep architecture. Patients under treatment with pregabalin had a greater improvement in IRLS score than under placebo (63% vs 38.2%; p <0.05). The mean effective dose of pregabalin at the end of treatment was 322.50 mg/day (98.77), although therapeutic effects were already seen at a mean dose of 139 mg/day. Similarly, improvements were observed on the CGI, RLS-6 scale, and the Medical Outcomes Study sleep scale (all p 0.01) when compared to placebo. Treatment with pregabalin also resulted in a reduction of the mean (±SD) PLM index (p<0.001). Furthermore, there was a marked improvement in sleep architecture with an increase in slow wave sleep (p <0.01), and decreases in wake after sleep onset and stages 1 and 2 (p <0.05).	This study shows significant therapeutic effects of pregabalin on both sensorial and motor symptoms in restless legs syndrome. Treatment with pregabalin was associated with an improvement of sleep architecture and periodic limb movements. Adverse events included unsteadiness and sleepiness and should be screened carefully in the working population, particularly when pregabalin is administered in the afternoon.	Placebo run in conducted: eliminated placebo responders
Grote, 2009 (102)	Criteria for inclusion were age between 18 and 70 years, 4 cardinal RLS diagnostic criteria,20 a score of 10 or more on the International Restless Legs Study Group Rating Scale (IRLS),21 a S-ferritin concentration below 30 lg/L and normal folic acid/ B12 vitamin serum values. A study amendment issued after inclusion of 30 patients increased the threshold for S-ferritin to 45 lg/L according to previously published recommendations.Exclusion criteria encompassed concomitant use of any drug treatment for RLS, clinical or laboratory findings suggestive of secondary RLS, any previously known clinically significant allergic reaction, use of drug treatment known to induce RLS, pregnancy or a specific contraindication for iron sucrose.	10+ on IRLS	60/(46)/7M 43F	Iron sucrose was generally well tolerated.	The primary efficacy variable was the RLS severity scale (IRLS) score at week 11. Median IRLS score decreased from 24 to 7 (week 11) after iron sucrose and from 26 to 17 after placebo (P 5 0.123, N.S. for between treatment comparison). The corresponding scores at week 7 were 12 and 20 in the two groups (P=0.017). Drop out rate because of lack of efficacy at 12 months was 19/31 after placebo and 5/29 patients after iron sucrose (Kaplan–Meier estimate, log rank test P= 0.0006) suggesting an iron induced superior long term RLS symptom control.	This study showed a lack of superiority of iron sucrose at 11 weeks but found evidence that iron sucrose reduced RLS symptoms both in the acute phase (7 weeks) and during long-term follow up in patients with variable degree of iron deficiency.	

Evidence Table
The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Inclusion/ Exclusion criteria	RLS Severity	Sample size (completed) / mean age (age range or standard deviation) / gender of subjects	Adverse effects	Outcome measures / results	Conclusions	Comments
Happe, 2003 (90)	Idiopathic RLS. A PLMS index of more than 5 and a complaint of either insomnia, excessive daytime sleepiness or both were also taken as inclusion criteria. Patients with any signs of another sleep disorder in their history or in polysomnography were excluded. Any severe additional disease and any signs of polyneuropathy were also taken as exclusion criteria. Pregnant or lactating women as well as women not using safe contraception were not allowed to take part in this study.	Not stated, but data indicates moderate	16 / Gabapentin: (mean age 56.0 ± 9.2 years, range 47–74 years; 5 women); Ropinirole: (mean age 63.4 ± 7.6 years, range 49–72 years; 6 women)	In the gabapentin group, there were only mild and mostly transient side effects such as numbness, dizziness, sleepiness and headache. Two patients reported ongoing side effects, 1 headache and 1 sleepiness, but these side effects were only mild and did not lead to discontinuation of gabapentin. In the ropinirole group, side effects such as nausea and sleepiness were also only mild and transient.	PSG (for PLMS index and arousal index), IRLSSG preliminary rating scale, ESS, QLI, PSQI, Zung depression and anxiety scales In both groups, IRLSSG questionnaire scores improved significantly ($p \leq 0.018$), whereas the scores of the Epworth sleepiness scale remained unchanged within normal limits. Polysomnographic data showed a reduction of periodic leg movements during sleep (PLMS; $p < 0.03$) and PLMS index ($p < 0.02$) in both groups. After 6–10 months of follow-up, in most patients, RLS symptoms were still improved.	We conclude that gabapentin and ropinirole provide a similarly well-tolerated and effective treatment of PLMS and sensorimotor symptoms in patients with idiopathic RLS.	
Hayes, 2008 (150)	Patients with concurrent moderate-to-very-severe RLS (IRLSSS ≥ 15) and duplex-proven SVI. Patients found to have greater than 500 ms of reflux in the great saphenous vein underwent a complete duplex evaluation of the deep, superficial and perforator systems. All reflux was mapped for appropriate treatment. Exclude the conditions that mimic RLS (such as positional discomfort, neuropathy, night cramps and so on). We did not exclude patients who were taking RLS medications. In order to stabilize RLS medication as a variable, we did ask patients not to add or discontinue medications known to affect RLS symptoms during the study period. All RLS patients with normal venous function were therefore excluded.	Moderate to very severe	35, 16 controls and 19 treatment (15 and 18) / Controls, 58.8 y and 6.3%M; Treatment, 49.4 y and 31.6%M	Duplex evaluation performed 6 weeks postoperatively and revealed that 100% of the treated veins were successfully ablated. Transient postoperative discomfort in the region of the treated veins was frequently reported. Most patients required only PRN Ibuprofen, foregoing the prescribed hydrocodone. All patients had mild bruising at the access sites. There were no major side-effects or complications.	Baseline and follow-up IRLS scores were compared. Operative correction of the SVI decreased the mean IRLS score by 21.4 points from 26.9 to 5.5, corresponding to an average of 80% improvement in symptoms. Controls: baseline = 26.8,f inal=28.4. A total of 89% of patients enjoyed a decrease in their score of ≥15 points. Fifty-three percent of patients had a follow-up score of ≤ 5, indicating their symptoms had been largely alleviated and 31% had a follow-up score of zero, indicating a complete relief of RLS symptoms.	ELA of refluxing axial veins with the CTEV 1320 nm laser and foamed STS sclerotherapy of associated varicosities alleviates RLS symptoms in patients with SVI and moderate to very severe RLS.	SVI should be ruled-out in all patients with RLS before initiation or continuation of drug therapy.
Hening, 2010 (110)	Baseline sum score ‡15 on the IRLSSG Severity Rating scale (IRLS13), and a score ‡4 at baseline for the clinical global impressions (CGI) item 1 assessment (severity of symptoms14). Subjects were excluded for secondary RLS	Moderate to severe	505 (494) / 52.4 (12.6) / 60% female	Skin reactions (27%) and known dopaminergic side effects such as nausea (18.1%) and headache (11.6%) were mostly mild or moderate in rotigotine subjects. AEs of severe intensity as rated by the investigator were observed for 19.6% rotigotine (13.1% for 0.5 mg/24 hr, 17% for 1 mg/24 hr, 27.3% for 2 mg/24 hr, and 20.8% for 3 mg/24 hr) and 12% placebo subjects. The majority of AEs resolved before the end of the trial (80% placebo and 83% rotigotine).	The two co-primary efficacy parameters decreased from baseline to end of maintenance in IRLS sum score and in clinical global impressions (CGI-1) score. On both primary measures, 2 and 3 mg/24 hr rotigotine was superior to placebo ($P < 0.001$). Adjusted treatment differences to placebo for the IRLS sum score were 24.5 (95% CI: 26.9, 22.2) for 2 mg/24 hr rotigotine, 25.2 (95% CI: 27.5, 22.9) for 3 mg/24 hr rotigotine, and for CGI item 1 20.65 (95% CI: 21.0, 20.3) and 20.9 (95% CI: 21.3, 20.5) for the 2 and 3 mg/24 hr doses, respectively.	Rotigotine transdermal patches releasing 2 to 3 mg/24 hr significantly reduced the severity of RLS symptoms. Treatment efficacy was maintained throughout the 6-month double-blind period	
Hogl, 2010 (61)	Idiopathic RLS. The study was designed to include patients who had never before been treated with dopaminergic drugs (levodopa, dopamine agonists), who were aged between 18 and 80 years. Patients were excluded from the study if RLS symptoms at baseline occurred before 6 p.m. Further exclusion criteria included other severe primary sleep disorders, neurological, psychiatric, and pain disorders or severe medical and surgical conditions, as well as clinically relevant laboratory abnormalities.	Severe	65 (60 provided evaluable data, 35 completed the trial, 25 dropped out) / 52.6 ± 12.8 / 22M 38F	Three patients discontinued the study prematurely due to adverse events, two augmenters (subjectively reported impaired cognitive ability in one patient, impaired coordination and emotional disturbance in the other), and one patient without augmentation due to tiredness during the day, nausea and nightmares.	In addition to the augmentation severity rating scale (ASRS), changes in RLS severity (International RLS severity rating scale (IRLS) and RLS-6, clinical global impression (CGI)) were analyzed. Other outcome measures were treatment satisfaction as measured with the treatment satisfaction questionnaire for medication (TSQM), and quality of life (RLS quality of life instrument (RLS-QLI)). Augmentation occurred in 60% (36/60) of patients, causing 11.7% (7/60) to drop out. Median time to occurrence of augmentation was 71 days. Patients with augmentation compared to those without were significantly more likely to be on higher doses of levodopa (≥300 mg, 83 vs. 54%, P = 0.03) and to show less improvement of symptom severity (IRLS, P = 0.039).	Augmentation was common with levodopa, but could be tolerated by most patients during this 6-month trial. Patients should be followed over longer periods to determine if dropout rates increase with time. This study confirms the high risk for augmentation during levodopa therapy of RLS patients. Augmentation was diagnosed in 60% of all analyzable patients and occurred at all doses of levodopa between 50 and 500 mg/day. Furthermore, augmentation could occur at any time during the 6 month treatment period and its prevalence increased progressively with time. In addition, its severity also increased with the duration of levodopa therapy.	
Hogl, 2010 (113)	Partcipants in the SP709 trial	Moderate to severe	310 eligible; 295 entered; 190 completed / 58.3 ± 10.1 years (range 22-75) at baseline / 66% females	Rotigotine was generally well tolerated. The rate of typical dopaminergic side effects, nausea and fatigue, was low (0.9% and 2.3%, respectively) during the second year; application site reactions were frequent but lower than in year 1 (16.4% vs. 34.5%).	The IRLS total score improved from baseline of SP709 (27.8 ± 5.9) by 17.2 ± 9.2 in year 2 completers. Similar improvements were observed in RLS-6 scales, CGI scores and QoL-RLS. The responder rate in the CGI change item 2 ("much" and "very much" improved) was 95% after year 2.	Transdermal rotigotine is an efficacious and well-tolerated long-term treatment option for patients with moderate to severe RLS with a high retention rate during 2 years of therapy.	16% Withdrawals in year one were due to AEs; 7% in year 2
Hornyak, 2008 (130)	Patients with subjective psychosocial impairment due to RLS. The severity scales (IRLS and RLS-6) indicated moderate to severe RLS symptoms at baseline. For inclusion, patients must have reported in the clinical interview bothersome psychosocial impairment due to RLS. Both medicated and unmedicated patients were included in the study. Some of the medicated patients did not wish a further increase in dose. In other cases, a further increase in dose or a change of dopamine agonists or add-on therapies (eg, opiates) led to barely tolerable side effects. Exclusion criteria were secondary RLS (due to an underlying disorder known to trigger RLS, eg, renal failure, autoimmune disorders) serious physical comorbidity with possible deterioration of quality of life (eg, neurodegenerative disorders, active malignant tumours), serious psychiatric comorbidity (eg, severe depression with suicidality, post-traumatic stress disorder, substance dependency) and severe cognitive deficits	Moderate to severe	25 at 8 weeks; 23 at follow up / 56.1 (12.3) / 5M20F	Not described	The primary outcome measure was the change in the RLS-specific quality of life (QoL-RLS)12 total score. At the end of the treatment, both the RLS-related quality of life and the mental health status of the subjects had improved significantly (QoL-RLS scale: from 28.6 (12.8) to 23.4 (13.1); SCL-90-R: from 51.3 (37.0) to 45.9 (32.9)). The improvement remained at follow-up 3 months later. Subjective ratings of RLS severity had improved at the end of therapy and at follow-up. Psychometric scales not specific for RLS-related impairment remained unaffected by the treatment. IRLS total 25.9 (6.9) to 19.1 (6.3), p<0.001 at 8 weeks and 3.0 (2.6) at F/U; RLS-6 at bedtime baseline 5.2 (3.3) to 3.1 (2.7), p=0.008 and 3.0 (2.6) at F/U	The study establishes the feasibility and high acceptance of the newly devised therapy programme. The application of RLS-oriented specific psychological strategies is a step toward an integrated treatment approach in RLS.	Patients ranked as most helpful (in descending order) the mindfulness-based exercises (including breathing exercises), stress reduction strategies, diary-based analysis of factors aggravating RLS, and medical education.
Inoue, 2010 (34)	Male and female patients enrolled in this study were between 20 and 80 years old. The diagnosis of primary RLS was made according to the essential criteria of the International Restless Legs Syndrome Study Group (IRLSSG) [9] by a sleep disorders expert physician with experience in diagnosis and therapy of RLS. For enrollment in the study, patients were required to have a total score of at least 15 on the IRLSSG rating scale (IRLS) [9], PLM at least five times per hour at a time in bed as documented by baseline polysomnography (PSG) weekly RLS symptoms that had disrupted nocturnal sleep within the previous month. Patients who were treated with medications or dietary supplements that might possibly influence RLS symptoms within 14 days before administration of the study medication were excluded. Premenopausal women who were pregnant or possibly pregnant, who were lactating or had the desire to become pregnant during the study period, and men who did not use an adequate form of contraception were also excluded. Regarding, comorbid conditions, patients with diabetes mellitus requiring insulin therapy, microcytic anaemia (at the investigator's discretion), possible presence of other sleep disorders, and any other neurological diseases with potential to cause secondary RLS were excluded.	Moderate to severe; total score of at least 15 on the IRLSSG rating scale (IRLS)	41 (37) /48.7 ± 16.1 for pramipexole 62.3 ± 11.9 for placebo/ 20M 21F	Overall, pramipexole was tolerated well and no major differences were found for overall incidence of adverse events between the pramipexole group (80.0%) and the placebo group (66.7%). Gastrointestinal disorders were more common in the pramipexole group (55.0%) than in the placebo group (28.6%). The most frequent adverse events were nausea (25.0% pramipexole, 9.5% placebo), upper abdominal pain (15.0% pramipexole, 4.8% placebo), and stomach discomfort (15.0% pramipexole, 0.0% placebo). In the system organ class "nervous system disorders," the most frequent adverse events were headache (15.0% pramipexole, 9.5% placebo) and somnolence (10.0% pramipexole, 14.3% placebo). Other frequently reported adverse events were nasopharyngitis (25.0% pramipexole, 4.8% placebo) and fatigue (10.0% pramipexole, 0.0% for placebo) (Table 4). Drug-related adverse events that occurred more frequently in the pramipexole group than in the placebo group were nausea (15.0% pramipexole, 4.8% placebo), stomach discomfort (15.0% pramipexole, 0.0% placebo), and headache (10.0% pramipexole, 0.0% placebo). Only for nausea, the frequency of the onset increased along with the dose level (0.0% with 0.125 mg/day, 5.0% with 0.25 mg/day, 5.0% with 0.5 mg/day, and 10.5% with 0.75 mg/ day). No patients were withdrawn from the study because of an adverse event in either treatment group. No clinically significant changes in any clinical laboratory tests, vital signs, or electrocardiography findings were observed in the pramipexole group. One patient in the pramipexole group experienced a serious adverse event, ileus adhesive which was assessed to be unrelated to thestudy medication by the investigator.	**IRLS** In the pramipexole group, the mean (SD) of IRLS total score was reduced from 23.4 (6.4) at baseline to 12.4 (6.9) at week 1, 11.2 (7.4) at week 2, 7.4 (7.8) at week 4, and finally 7.3 (8.1) at week 6. In the placebo group, it was reduced from 25.1 (5.8) at baseline to 19.8 (6.9) at week 1, 19.7 (7.5) at week 2, 18.1 (9.7) at week 4, and finally 18.7 (9.1) at week 6. Statistically significant differences were noted after 1, 2, 4, and 6 weeks of treatment between the pramipexole group and the placebo group ($p < 0.001$, **Data reported versus baseline:** PSG PLMI: -23 for pramipexole and -6 for placebo SIT PLM Index: no difference either group PGI: much improved or very much improved, proportion of patients was 95.0% for pramipexole and 38.1% for placebo ESS: no change for either group PSQI: stat sig difference in mean change between 2 groups CGI-I: 80.0% for pramipexole and 52.4% for placebo, stat sig	The extent of PLMI reduction in the pramipexole group of this study (approximately 85%) was very similar to those in the PRELUDE study (75–85% in the pramipexole groups) [10]. Among the secondary endpoints in other PLM parameters of this study, pramipexole was significantly superior to placebo for median changes of PLMSI, total number of PLM, and total number of PLM during sleep.	
Inoue, 2010 (38) (Neurology)	Male and female patients aged 20–80 years with a diagnosis of primary RLS based on the four IRLSSG essential criteria and an IRLSSG severity rating scale (IRLS) [1] total score N15 were eligible for inclusion Patients who had been taking medications or dietary supplements that could possibly influence RLS symptoms within 14 days before starting the study drug were excluded, as were premenopausal women who were pregnant or possibly pregnant, lactating, or considering becoming pregnant during the study period, as well as patients with diabetes mellitus requiring insulin therapy, microcytic anemia (at the investigators' discretion), possible presence of other sleep disorders, and any other neurological disorder with potential to cause secondary RLS.	IRLS avg score: 22.3±4.7 (modereate to severe)	141 (123) / 52.6±14.0 (<55, n=74; ≥55, n=66) / Males: 61 (43.6%) Females: 79 (56.4%)	87.9% of patients experienced Aes. Adverse events were typical of nonergot dopamine agonists, mild in intensity, and decreased in frequency as the study progressed. RLS augmentation was not observed.	IRLS score improved from 22.3±4.7 at baseline to 11.1±7.7 at week 8 and 4.9±5.9 at week 52. IRLS responders, defined as patients whose IRLS total score decreased by ≥50% from baseline, accounted for 67.4% at week 12 and 86.6% at week 52. Over 90% of patients were Clinical Global Impression-global improvement (CGI-I) and Patient Global Impression (PGI) responders. The Pittsburgh Sleep Quality Index (PSQI) score decreased from 7.9±3.1 at baseline to 4.6±2.9 at week 52. Similarly, the Japanese version of the Epworth Sleepiness Scale score decreased from 9.3±5.2 to 4.9±3.8.	Efficacious, safe, well tolerated, noted to be particularly effective in patients with IRLS<20	

Evidence Table
The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Inclusion/ Exclusion criteria	RLS Severity	Sample size (completed) / mean age (age range or standard deviation) / gender of subjects	Adverse effects	Outcome measures / results	Conclusions	Comments
Jama, 2009 (35)	Adult patients (≥18 years of age) with idiopathic RLS were eligible for the study. Inclusion criteria included the presence of all 4 international RLS study group criteria for the diagnosis of RLS; moderate or severe symptoms, defined as a score of ≥15 on the international RLS study group rating scale (IRLS); a PLM frequency ≥5 times/h during time in bed, documented by polysomnography; and weekly sleep disturbances due to RLS within the prior 3 months. Exclusion criteria included any of the following: the presence of contraindications to the use of pramipexole; the presence or evidence of other sleep disorders, substance abuse, or comorbid conditions that may cause or exacerbate RLS or interfere with its assessment; the use of medications that may influence the course of RLS; participation in an investigational drug study within the previous 2 months; and current use (within the previous week) of any RLS therapy. Pregnancy or breast-feeding were also causes for exclusion, and females of childbearing potential and males were required to use adequate contraception.	Moderate or severe symptoms, defined as a score of ≥15 on the international RLS study group rating scale (IRLS)	109(107) /53 placebo, 58 for pramipexole at 0.5 mg / 79F 28M	The overall incidence of adverse events was similar across all treatment groups (placebo, 77.3%; pramipexole 0.125 mg, 81.0%; pramipexole 0.25 mg, 77.3%; pramipexole 0.50 mg, 81.8%; and pramipexole 0.75 mg, 59.1%). Combining all pramipexole groups, the incidence of adverse events was minimally lower among pramipexole-treated patients (74.7% vs. 77.3% with placebo). Adverse events that occurred with a higher incidence in the placebo group than in the combined pramipexole groups were fatigue (22.7% vs. 18.4%, respectively), headache (31.8% vs. 19.5%, respectively), and insomnia (9.1% vs. 0%, respectively). The adverse events that were reported more frequently in the combined pramipexole groups than with placebo included nausea (14.9% vs. 4.5%, respectively), nasopharyngitis (6.9% vs. 0%, respectively), flu-like symptoms (4.6% vs. 0%, respectively), and worsening of RLS (4.6% vs. 0%, respectively).	For the primary endpoint of PLMI, all pramipexole doses demonstrated a reduction in median PLMI that was significantly greater than that with placebo ($p < 0.01$) using the Wilcoxon–Mann–Whitney test. Consistently larger treatment effects were also observed with pramipexole compared with placebo for median change from baseline in the secondary objective endpoints of PLMSI and PLMWI. For PLMI, PLMSI, and PLMAI, the proportion of patients with a normalized index (<5/h) after 3 weeks was significantly greater with pramipexole than with placebo (41.9% vs. 0%, respectively, for PLMI [$p = 0.0003$]; 65.1% vs. 19.0%, respectively, for PLMSI [$p = 0.0001$]; and 82.6% vs. 33.3%, respectively, for PLMAI [$p < 0.0001$]). Subjective RLS assessments using the IRLS were consistent with the PLM-index findings. As shown in Fig. 3A, treatment with all pramipexole doses was associated with a marked median reduction in the total number of PLM and the total number of PLM during sleep.	Pramipexole is effective and well tolerated in RLS, most notably among objective measures, for reducing PLM and decreasing sleep latency. Although other sleep parameters showed lesser, usually insignificant change, patients' subjective ratings of RLS severity and sleep disturbance were significantly improved (p 6 0.0023).	
Kim, 2008 (126)	The inclusion criterion was patients with any psychiatric disturbance who received mirtazapine as treatment from either of two psychiatrists (S.W.K. or I.S.S) who were experienced in the diagnosis and management of RLS. The criterion for exclusion was the lack of follow-up information.	N/A	205 charts reviewed; 181 charts included / 59.2 years (SD, 13.3; range, 18–84 years) / 62% Female	Twenty-eight patients (15%) stopped taking mirtazapine because of tolerance problems. Among them, 23 patients (82%) stopped medication within 1 month.	Mirtazapine-associated RLS was observed in 14 patients (8%), and most cases had developed within a few days after starting mirtazapine. Concomitant medication with tramadol, non-opioid analgesics, antihistamine, and dopamineblocking agents was more frequently prescribed in subjects developing mirtazapine-associated RLS. In logistic regression analysis, concomitant medication with tramadol (odds ratio: 8.61, 95% confidence interval: 1.71–43.49) and dopamineblocking agents (odds ratio: 4.67, 95% confidence interval: 1.31–16.70) enhanced the risk of mirtazapine-associated RLS.	The combined use of mirtazapine with tramadol or dopamine-blocking agents could potentiate the risk of RLS. Clinician should watch carefully for the development of RLS when mirtazapine is administered to patients who are taking tramadol or dopamine-blocking agents.	
Kunz, 2001 (152) **PLMD**	First time diagnosis of PLMD without RLS. Patients with RLS were excluded for two reasons. Firstly, even though occurrence of PLMD and RLS seem to be closely linked, both of their pathologies are not yet known. Thus, a bias could have been introduced. Secondly, discomfort in RLS induces movements, which could never be differentiated in actigraphy from PLMs. 4 patients met the criteria for severe PLMD (PLM index > 50), three for moderate (PLM index 26 thru 50), and two for mild (PLM index 5 thru 25) PLMD.	N/A	9 (3 female, 6 male; mean age 57 years, range 40 through 71 years)	Not reported	PSG, 24-item validated Zerssen well-being scale, sleep diaries, actigraphy Melatonin improved well-being in 7 of the 9 patients. The two nonresponding patients were noncompliant with respect to the time of melatonin administration, changing several hours from day to day.Polysomnography, performed prior and at the end of melatonin treatment, demonstrated a significant reduction of investigated movement parameters, such as PLMs, PLM index, PLMs with arousals and PLM-arousal index. Actigraphy, measured over 14 nights prior and during the last 14 days of melatonin treatment, showed a significant reduction in movement rate and minutes with movements during Time in Bed.	The presented data shows that melatonin, administered to PLMD patients over a six-week period, significantly improved clinical symptoms of PLMD. The improvement was polysomnographically and actigraphically substantiated by a significant reduction of measured movement parameters, such as PLMs, PLMs with arousal, PLM index, PLM-arousal index, movement rate, and the proportion of minutes TIB with movements.	Since this was an open-labeled study, results need to be considered as preliminary. Nevertheless, because of low toxicity of melatonin, we suggest that melatonin might exert beneficial effects in PLMD patients.
Kushida, 2008 (54)	Patients with early evening (onset no earlier than 5 PM) primary RLS symptoms and a a baseline IRLSGRS total score ≥ 20. Patients were eligible for inclusion if they were aged 18 to 79 years, a baseline score ≥ 20 on the IRLS, a baseline score ≥ 15 on the Insomnia Severity Index, symptom onset no earlier than 5 PM (and prior to the onset of bedtime), and at least 15 nights of RLS symptoms during the previous month. Patients were excluded if they were suffering from other primary sleep disorders, movement disorders, or medical conditions that could affect the assessment of RLS; if they were experiencing daytime RLS symptoms that required treatment; if they were taking medications known to affect RLS or sleep; or if they were experiencing withdrawal/ introduction/dose change of medications known to inhibit or induce P450 CYP1A2. Patients experiencing signs of secondary RLS (eg, end-stage renal disease, iron deficiency, or pregnancy) were excluded, as were patients who had experienced augmentation or rebound with previous treatment.	IRLS≥20 (at least severe)	175 ropinirole, 184 placebo /	The most frequently reported adverse events (AEs) were nausea, headache, somnolence and vomiting. The number of patients who withdrew due to AEs was low and similar between treatment groups (Table 1). In total, 5 patients reported a serious AE (ropinirole, n = 2; placebo, n = 3), none of which were considered by the investigator to be related to the study drug.	Primary end point: change from baseline in IRLS total score at week 12 last observation carried forward (LOCF). Key secondary end points: proportion of responders (rated "very much improved" or "much improved") on the Clinical Global Impression-Improvement and the Patient Global Improvement scales. Improvements in IRLS total score were statistically significantly greater for ropinirole, compared with placebo at all assessment points beginning at day 3 through to week 12 LOCF ($P <$ 0.001). [From figure: placebo change -11 (2SE from -9 to -13) and ropinirole -15 (2SE from -13.5 to -16.5), (adjusted mean treatment difference:-4.11; 95% confidence interval [CI]:-6.08, -2.14; $P < 0.001$). A statistically significantly greater proportion of patients were classified as responders on the Clinical Global Impression-Improvement scale at all assessment points from day 3 through week 12 LOCF ($P < 0.001$) and on the Patient Global Improvement scale at all assessment points from day 1 ($P = 0.013$) through day 7 LOCF ($P \leq 0.05$ for days 2-7 LOCF) and at week 12 LOCF ($P < 0.001$).	Ropinirole is associated with consistent early and sustained improvements in the symptoms of RLS, as rated by patients and physicians. COMMENT: SIGNIFICANT PLACEBO EFFECT	The study reported here is distinct from prior studies in that it investigated the effect of ropinirole (0.5-6.0 mg/d) given twice daily in 2 equally divided doses, in patients with early evening symptoms, with a particular focus on patient-rated improvements. Physician-rated assessments of symptoms and treatment outcomes are also presented.
Kushida, 2009 (92) **Clinical trials.gov identifier NCT00298623 PIVOT RLS-I**	Inclusions: Men and women ≥ 18 years; moderate-to-severe primary RLS; RLS symptoms ≥15 days during the month prior to screening (or, if on treatment, similar symptom frequency before treatment initiation) and symptoms on ≥ 4 nights during the 7-day baseline period. Prior RLS treatment was discontinued at least 2 weeks prior to baseline; IRLS total score ≥ 15 at the beginning and end of the baseline period. Exclusions: evidence of secondary RLS; a BMI ≥ 34 kg/m^2; currently experiencing or being treated for moderate to severe depression, other primary sleep disorders, or neurologic disease or movement disorders; or had a history of RLS symptom augmentation or end-of-dose rebound with previous dopaminergic treatment; pregnancy. Although presence of daytime RLS symptoms (between 10:00 AM and 6:00 PM) for ≥ 2 days during the week prior to baseline was originally an exclusion criterion, this restriction was removed after enrollment of approximately 30% of the total study population to improve the generalizability of study results.	Moderate to severe	222 (192) / 51.1 (12.80) / 89M 132 F	The most commonly reported adverse events were somnolence (XP13512 27%, placebo 7%) and dizziness (XP13512 20%, placebo 5%), which were mild to moderate in intensity and generally remitted.	Coprimary endpoints were mean change from baseline IRLS total score and proportion of investigator-rated responders (very much improved or much improved on the Clinical Global Impression– Improvement scale) at week 12 (last observation carried forward). Tolerability was assessed using adverse events, vital signs, and clinical laboratory parameters. At week 12, the mean change from baseline IRLS total score was greater with XP13512 (-13.2) compared with placebo (-8.8). Analysis of covariance, adjusted for baseline score and pooled site, demonstrated a mean treatment difference of -4.0 (95% confidence interval [CI], -6.2 to -1.9; $p = 0.0003$). More patients treated with XP13512 (76.1%) were responders compared with placebo (38.9%; adjusted OR 5.1; 95% CI, 2.8 to 9.2; $p < 0.0001$). Significant treatment effects for both coprimary measures were identified at week 1, the earliest time point measured.	XP13512 1,200 mg, taken once daily, significantly improved restless legs syndrome (RLS) symptoms compared with placebo and was generally well tolerated in adults with moderate to severe primary RLS	
Kushida, 2009 (86) **The XP021 Study Group**	Moderate-to-severe primary RLS. Treatment naïve. Men and women, aged 18 to 69 years, RLS symptoms on at least 15 nights during the month prior to screening, documented RLS symptoms on at least 4 nights during the 7-day baseline period, and an IRLS total score of at least 15 at both the beginning and end of the baseline period. Enrolled subjects were otherwise healthy and free from clinically significant illness or disease. Exclusions: Daytime RLS symptoms (10:00- 18:00) for at least 2 days during the week prior to baseline; pregnancy; a BMI > 32 kg/m^2, an estimated creatinine clearance < 60 mL/ minute, or a serum ferritin level < 20 µg/mL or were currently experiencing or being treated for moderate-to-severe depression, a primary sleep disorder other than RLS, or any other serious neurologic disease or movement disorder. Dopamine agonists, levodopa/carbidopa, gabapentin, and medications used to treat sleep disorders were prohibited.	Moderate to severe	38 (34) / (mean ± SD age 50.1 ± 13.2 years) / 16M 22F	The most frequently reported adverse events were somnolence (XP13512 30.6%, placebo 2.8%) and dizziness (XP13512 27.8%, placebo 5.6%). XP13512 was generally well tolerated during this study. The most commonly reported AEs were somnolence and dizziness, both of which are consistent with the known profile of oral gabapentin. The short treatment period did not allow for an assessment of long-term tolerability with XP13512. No serious AEs were reported, and the only treatment discontinuation occurred with placebo.	The primary endpoint was mean change from baseline IRLS total score on Day 14, analyzed using analysis of variance with sequence, period, and treatment as fixed effects and subjects within sequence as a random effect. XP13512 significantly reduced IRLS total score on Day 14 compared with placebo (mean ± SD: XP13512 -12.1 ± 6.5, placebo -1.9 ± 6.3; $P <$ 0.0001). Polysomnographic data showed that XP13512 significantly improved sleep architecture on Day 14 compared with placebo (mean ± SD change from baseline sleep time [minutes]: stage 1: XP13512 -9.8 ± 23.9, placebo 0.4 ± 23.2; adjusted $P < 0.0054$, nominal $P < 0.0001$; stage 3/4 (slow-wave sleep): XP13512 22.8 ± 40.8, placebo 1.4 ± 34.3; adjusted $P = 0.0092$, nominal $P = 0.0002$).	XP13512 1800 mg/day significantly reduced RLS symptoms, improved sleep, and was generally well tolerated in subjects with moderate-to-severe primary RLS across 14 days of treatment. In summary, results from this crossover study demonstrate that XP13512 has promising efficacy and tolerability as a nondopaminergic treatment for subjects with moderate to severe primary RLS . Subjects were at the target XP 13512 dose for only 2 days when improvements in IRLS score separated significantly from placebo at the earliest time point examined. These results suggest that lower doses with XP13512 should be explored.	
Lauerma, 1999 (78)	Some treatment resistent or prone to side effects. All patients reported distressing insomnia. 8 cases were familial.	Not stated ("at least minimal criteria" proposed by IRLS group)	12 / 56.6 (29-78) / 8F 4M	Tramadol was described as free of side effects compared to other treatments. No major tolerance against treatment effect emerged among those who needed only a single evening dose. 1 pt reported severe abdominal pain on 100 mg that resolved on 50 mg. 1 pt reported slight and transient morning dizziness and 2 experienced transient feelings or tremor. 1 pt experienced mild itching sensation.	Author-developed rating scale of overall severity, 0-100. 10 patients reported tramadol more effective than drugs tried in the past, 1 felt some relief, and 1 felt no relief. 7 reported total or almost total disappearance of symptoms. Some fading of drug effect over time reported. Some patients alternate with levodopa or clonazepam; some take "drug holidays" or use intermittently. Clear effect within 1 hr of ingestion.	Compared with other treatments, tramadol seems to be superior in some cases. We are impressed by the sustained effect in patients either who initially have been resistant to other medications or who, after good primary response, have suffered from complications when using levodopa, the most effective medication to date. We recommend intermittant use and minimizing the dose taken in the evening.	Controlled studies are needed.

Evidence Table
The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Inclusion/ Exclusion criteria	RLS Severity	Sample size (completed) / mean age (age range or standard deviation) / gender of subjects	Adverse effects	Outcome measures / results	Conclusions	Comments
Lee, 2011 (85)	Eligible subjects had RLS symptoms for ≥ 15 nights in the month prior to screening (or, if on treatment, the same frequency of symptoms before treatment was started), documented RLS symptoms for ≥ 4 of the 7 consecutive evenings/nights during the baseline period, an International Restless Legs Scale (IRLS)22 total score ≥ 15 at the beginning and end of the baseline period, and had discontinued dopamine agonists, gabapentin and any other RLS treatments for ≥ 2 weeks prior to baseline. No information was collected regarding patients' previous response to treatments. The rationale for a homogeneous patient population resulted in the exclusion of subjects if they had a history of RLS symptom augmentation or end-of-dose rebound with previous dopamine agonist treatment. Subjects were also excluded if they had a body mass index of > 34 kg/m2, an estimated creatinine clearance of < 60 mL/min or serum ferritin level of < 20 ng/mL, were currently suffering from moderate or severe depression, a neurologic disease, a sleep disorder, or a movement disorder other than RLS. Other exclusion criteria were clinically significant or unstable medical conditions, or other medical conditions or drug therapy which could have affected RLS treatment efficacy. Subjects were also excluded if they were pregnant or lactating.	Moderate to severe	325 subjects were randomized (GEn 1200 mg = 113; 600 mg = 115; placebo = 97).	The most commonly reported adverse events were somnolence (GEn 1200 mg = 18.0%; 600 mg = 21.7%; placebo = 2.1%) and dizziness (GEn 1200 mg = 24.3%; 600 mg = 10.4%; placebo = 5.2%). Dizziness increased with increased dose and led to discontinuation in 2 subjects (GEn 1200 mg, n = 1; GEn 600 mg, n = 1). Somnolence led to discontinuation in 3 subjects (GEn 600 mg).	Co-primary endpoints: mean change from baseline in International Restless Legs Scale (IRLS) total score and proportion of responders (rated as "very much" or "much" improved) on the investigator-rated Clinical Global Impression–Improvement scale (CGI-I) at Week 12 LOCF for GEn 1200 mg compared with placebo. Secondary endpoints included GEn 600 mg compared with placebo on the IRLS and CGI-I at Week 12 LOCF and subjective measures for sleep. Safety and tolerability assessments included adverse events. GEn 1200 mg significantly improved mean [SD] IRLS total score at Week 12 LOCF (baseline: 23.2 [5.32]; Week 12: 10.2 [8.03]) compared with placebo (baseline: 23.8 [4.58]; Week 12: 14.0 [7.87]; adjusted mean treatment difference [AMTD]: –3.5; p = 0.0015), and significantly more GEn 1200 mg-treated (77.5%) than placebotreated (44.8%) subjects were CGI-I responders (p < 0.0001). Similar significant results were observed with GEn 600 mg for IRLS (AMTD: –4.3; p < 0.0001) and CGI-I (72.8% compared with 44.8%; p < 0.0001). GEn also significantly improved sleep outcomes (Post-Sleep Questionnaire, Pittsburgh Sleep Diary and Medical Outcomes Sleep Scale) compared with placebo.	GEn 1200 mg and 600 mg significantly improve RLS symptoms and sleep disturbance compared with placebo and are generally well tolerated.	
Lettieri, 2009 (131)	All subjects were recruited from a single center, an academic, military referral hospital which serves military service members, retired members, and civilian dependents. Our patient population, therefore, is comprised of both men and women of all ages, and a wide spectrum of ethnic backgrounds. We excluded individuals < 17 years old; those with mental or physical limitations that would preclude data collection on questionnaires; and those with medical conditions that would preclude the use of PCDs, such as known or suspected deep vein thrombosis, active skin infections, recent vein ligation or skin graft, or extreme deformity of the legs. We also excluded individuals if they had previously used PCDs for deep vein thrombosis prophylaxis, as this would have potentially unblinded subjects randomized to sham devices.	IRLS 14.1 ± 3.9 (moderate)	35 / 47.8 ± 8.4 sham; 53.2 ± 9.8 therapeutic / 50% F Sham; 66.7% F therapeutic	No subjects reported a need to initiate or escalate medical therapy, none reported a worsening of their RLS symptoms, and none experienced any adverse reactions related to PCD use.	Measures of severity of illness (IRLSSS, JHRLSS), quality of life (RLS-QLI), daytime sleepiness (ESS), and fatigue (Fatigue Visual Analog Scale) were compared at baseline and after 1 month of therapy. Therapeutic PCDs significantly improved all measured variables more than shams. Restless Legs Severity Score improved from 14.1 ± 3.9 to 8.4 ± 3.4 (p = 0.006) and Johns Hopkins Restless Legs Scale improved from 2.2 ± 0.5 to 1.2 ± 0.7 (p = 0.01). All quality of life domains improved more with therapeutic than sham devices (social function 14% vs 1%, respectively, p = 0.03; daytime function 21% vs 6%, respectively, p = 0.02; sleep quality 16% vs 8%, respectively, p = 0.05; emotional well-being 17% vs 10%, respectively, p = 0.15). Both Epworth sleepiness scale (6.5 ± 4.0 vs 11.3 ± 3.9, respectively, p = 0.04) and fatigue (4.1 ± 2.1 vs 6.9 ± 2.0, respectively, p = 0.01) improved more with therapeutic devices than sham devices. Complete relief occurred in one third of subjects using therapeutic and in no subjects using sham devices.	PCDs resulted in clinically significant improvements in symptoms of RLS in comparison to the use of sham devices and may be an effective adjunctive or alternative therapy for RLS. Notably, one third of subjects using therapeutic PCDs experienced complete resolution of symptoms.	Clinicaltrials.gov Identifier: NCT00479531
Micozkadioglu, 2004 (135)	Hemodialysis patients. The ethologies of chronic renal failure (CRF) were: glomerulonephritis 3, pyelonephritis 3, hypertension 2, diabetes mellitus 1, polycystic kidney disease 1, preeclampsia 1, Fabry disease 1, amyloidosis 1, and unknown etiology, 2 patients.	From data, moderate	15 (14) / mean age of 45.8±15.3 years / 5 F, 10M	One of the patients had severe gabapentin-related side effects at the beginning and dropped out of the study.	Patients with RLS answered three questionnaires (RLS rating scale proposed by IRLSSG, the Short Form (SF)-36 and the Pittsburgh Sleep Quality Index) for the evaluation of severity of RLS, effects on quality of life and quality of sleep. When we compare the two drugs for severity of RLS symptoms relief, the effect of gabapentin was more significant (p<0.001). Gabapentin significantly improved general health, body pain and social functions (p<0.001). Moreover, regarding sleep parameters, gabapentin was significantly superior to levodopa for sleep quality, sleep latency (p<0.001) and sleep disturbance (p<0.000).	Our results suggested that gabapentin is an effective drug for the management of RLS in hemodialysis patients.	
Miranda, 2004 (138)	Severe enough to interfere with dialysis: They needed to be disconnected most of the time to relieve symptoms	Severe enough to interfere with dialysis: They needed to be disconnected most of the time to relieve symptoms	172 patients screened; 10 patients studied / mean age 48.4 years, range 36 to 66 years / 60% women	Pramipexole was well tolerated, with no patients requiring domperidone.	Primary outcome variables were the index of periodic leg movements of sleep (PLMS) and the index of periodic leg movements while awake (PLMW). Sleep efficiency, sleep latency, and total sleep time were secondary measures. Also IRLSSG Nine patients showed a response to pramipexole evident during the first week of treat-ment with a mean dose of 0.25 mg (range 0.125 to 0.5 mg). The mean score in the severity scale fell from 25.8 ± 5.75 (in the severe range) in the pretreatment evaluation to 7.7 ± 8.36 after treatment (p < 0.005). Eight patients were assessed with PSG following pramipexole. The variables that showed a response were the PLMS index, which fell from a mean of 108.7 ± 42.38 in the pretreatment PSG to 38.4 ± 27.46 in the posttreatment PSG (p < 0.001), and the PLMW index, which fell from a mean of 111.2 ± 40.99 to 42.4 ± 43.68 (p < 0.004) (table). Sleep latency, total hours of sleep, number of awakenings, and sleep efficiency showed no significant change.	Pramipexole may be effective in the treatment of uremic RLS patients in dialysis with no important adverse effects.	
Montagna, 2011 (36)	RLS-related mood disturbance at baseline (score ≥ 2 on Item 10 of IRLS). Patients with a baseline Beck Depression Inventory-II (BDI-II [19]) score >28, with current presence of major depression, psychosis, or any other severe mental disorder requiring medical therapy, or with any history of suicidal ideation (e.g., a BDI-II item 2 scoreP2 or item 9 score >0) were excluded from the study. Patients were also excluded for any clinical condition that could interfere with study participation or evaluation of results, or that could increase the patient's health risks. Concomitant or prior treatment (within 2 weeks) with any drug that could influence RLS symptoms or depressive symptoms (e.g., anxiolytics or hypnotics) was forbidden. Antidepressant use was not permitted within 6 weeks of baseline, nor was withdrawal of antidepressants permitted for the purpose of study entry. Women with childbearing potential were required to use adequate contraception, and pregnant or breastfeeding women were excluded.	Moderate to very severe	ITT was 199 placebo and 203 pramipexole / 56.1±12.1 for placebo and 55.0±13.8 for pramipexole / 73% female for placebo and 67% female for pramipexole	Study withdrawal rates were higher for placebo (20.5%) than for pramipexole (12.8%). The overall incidence of AEs was 61.1% in the pramipexole group and 51.5% in the placebo group.	–14.2 ± 0.7 for pramipexole and –8.1 ± 0.7 for placebo (p < 0.0001), and on the Beck Depression Inventory version II, –7.3 ± 0.4 for pramipexole and –5.8 ± 0.5 for placebo (p = 0.0199). For IRLS item 10, the 12-week responder rate (reduction to no or mild mood disturbance) was 75.9% for pramipexole and 57.3% for placebo (p < 0.0001).	In patients with RLS-related mood disturbance, pramipexole improved RLS while also improving RLS-related mood impairment. Tolerability of pramipexole was similar to that in previous studies.	
Montplaisir, 2006	A diagnosis of primary RLS; treatment with pramipexole initiated at least 12 months before; no history of previous treatment with DA medication (either levodopaor DA agonists); no other conditions known to be associated with RLS.	Overall, patients who continued pramipexole for more than 1 year, reported a mean decrease in RLS symptom severity of 80.0 ± 20.8% (n = 152) and 144 of 152 patients (94.7%) reported a decrease in severity of 50% or more at follow-up compared with baseline	195/31.0-87.1(55.1)/110F 85M	Patients who discontinued pramipexole: dizziness (n = 7), nausea (n = 5), sleepiness (n = 5), and insomnia (n = 3). Two patients complained of sleepiness at the wheel but no sudden onset of sleep occurred.	for patients who continued pramipexole:Two questions inquired separately about the effects of pramipexole on RLS symptom frequency and severity. The answers to these two questions were identical for all but one patient (151/152 or 99.3%). To avoid redundancy, only severity data will be presented here as a measure of efficacy. Overall, patients who continued pramipexole for more than 1 year, reported a mean decrease in RLS symptom severity of 80.0 ± 20.8% (n = 152) and 144 of 152 patients (94.7%) reported a decrease in severity of 50% or more at follow-up compared with baseline	In conclusion, the present study confirms, in a large cohort of DA drug-nai¨ve patients, that pramipexole is effective and safe in the long-term treatment of RLS.	
Montplaisir, 2006 (55)	Inclusions: Primary RLS, male or female 18 - 80 years from 18 centers in Australia, Austria, Canada, Germany, and South Africa, with a score of ≥15 on the IRLSSG's severity scale, a history of experiencing ≥ 15 nights of RLS symptoms during the previous month. Patients were excluded if they were suffering from symptoms of RLS that required treatment during the day, or from augmentation or end-of-dose rebound during previous therapy. Those patients suffering from a primary sleep disorder that might affect the symptoms of RLS, those patients with another movement disorder, or those patients with a medical condition that would affect the assessment of RLS or the tolerability of ropinirole were also excluded. In addition, patients taking taking any other medications known to affect sleep, those patients with a known intolerance to ropinirole, or patients meeting DSM-IV criteria for substance abuse/dependence were excluded. Phase 2 inclusion if response in Phase 1 (a reduction in the total IRLS score of at least 6 points from baseline).	IRLS≥15 (at least mid-moderate)	Phase 1: 202 / 52.9 ± 13.48 (18–79) / 121F.81M Phase 2, Ropinirole 45 / 51.6 ± 11.33 (23–70) / 21F 24M Phase 2, Placebo 47 / 55.3 ± 11.03 (25–78) / 30F 17M	Ropinirole was well tolerated; AEs were typical for dopamine agonists. A total of 184/202 patients (91.1%) reported an AE during phase 1. The most common AE was nausea; other frequent events considered to be possibly or probably related to ropinirole treatment included headache, fatigue, and dizziness. 3 patients on ropinirole had reports of hyperkinesia with the term "augmentation" noted. Most of the AEs were either mild or moderate in severity; 69 patients (34.2%) reported an AE that was classified as severe. Those severe events reported by more than 1% of patients were nausea (19 patients; 9.4%), vomiting (8 patients; 4.0%), headache and hyperkinesia (6 patients each; 3.0%), fatigue and back pain (5 patients each; 2.5%), diarrhea (4 patients; 2.0%), and dry mouth, pain, dizziness, migraine, paresthesia, somnolence, virus infection, and sinusitis (all symptoms, 3 patients; 1.5%).	The primary efficacy variable was the proportion of patients relapsing during double-blind treatment. Additional efficacy measures included time to relapse, withdrawals due to lack of efficacy, improvement on the Clinical Global Impression–Improvement (CGI-I) scale, change in International Restless Legs Scale (IRLS) score during doubleblind treatment, and changes in sleep and quality of life (QoL) parameters. Significantly fewer patients relapsed on ropinirole than on placebo (32.6% vs. 57.8%; P = 0.0156). Time to relapse was longer with ropinirole and more patients withdrew due to lack of efficacy with placebo. Patients showed improvements in IRLS and CGI-I scores, sleep and QoL parameters with single-blind ropinirole, which were better maintained when ropinirole was continued during the double-blind phase, but reduced with placebo.	Ropinirole was highly effective and well tolerated in the long-term management of RLS, with pharmacological effect over 36 weeks.	At week 20 of the single-blind treatment phase, after which no more changes in dose were allowed, the mean and median doses of ropinirole were 2.05 and 2.00 mg/day, respectively. At week 24, a total of 18 patients (15.8%) were receiving the maximum dose of ropinirole, 4.0 mg/day.

Evidence Table
The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Inclusion/ Exclusion criteria	RLS Severity	Sample size (completed) / mean age (age range or standard deviation) / gender of subjects	Adverse effects	Outcome measures / results	Conclusions	Comments
Oertel, 2006 (63)	Patients with moderate to severe RLS by an IRLS total score ≥ 10, RLS-6 severity at night ≥ 4, and PLMS-AI > 5/ hr TST. Exclusions: secondary RLS due to iron deficiency, renal disease, or drugs; evidence of mimics of RLS; idiopathic Parkinson disease, insulin-dependent diabetes mellitus, clinically relevant polyneuropathy, liver disease, history of sleep apnea, or malignancy, pleural effusions or fibrosis, and established or suspected hypersensitivity to ergot alkaloids; cabergoline pretreatment. Women were excluded if they were pregnant or lactating, or at risk for pregnancy. Concomitant use of drugs such as dopamine agonists, levodopa, neuroleptics, hypnotics, antidepressants, anxiolytics, anticonvulsants, psychostimulants, and opioids was prohibited between screening visit and final assessment; in addition, iron substitution or treatment with magnesium or antihistaminics was not permitted during the study. Inclusion was possible given a washout was performed with a duration of at least five half-lives of the respective medications.	Moderate to severe	43 patients were treated and 40 patients were evaluated with PSG (age 56 ± 10 years, 73% women).	Adverse events were only mild and well-known side effects of dopamine agonists.Three females discontinued participation during the first or second week because of adverse events. Pt 1 had severe vertigo, nausea, and moderate edema, which emerged at 1.0 mg. Pt2 had severe nausea and emesis at 1.5 mg. Pt3 with concomitant hypertension had severe chills, dizziness, and fatigue at 2.0-mg dose level, which and recovered immediately after discontinuation of the drug. More patients in the cabergoline group than in the placebo group were affected by adverse events. The events where the investigator suspected a relationship to treatment were known side effects of dopamine agonists: gastrointestinal symptoms, dizziness, fatigue, and vertigo. No serious adverse events were reported.	The primary efficacy measures were the periodic leg movements during sleep arousal index (PLMS-AI) and sleep efficiency. Severity of RLS was assessed using the International RLS Study Group Severity Scale (IRLS), the RLS-6 scales, the Sleep Questionnaire Form A (SF-A; quality of sleep), and the Quality of Life for RLS questionnaire. Cabergoline was superior to placebo in terms of the PLMS-AI (-17.7 ± 16.4 vs -4.5 ± 20.0 placebo; p = 0.0024), sleep efficiency (6.2 ± 13.9% vs 3.3 ± 11.7%; p = 0.0443), PLMS index (p = 0.0014), PLM index (p = 0.0012), and total sleep time (p = 0.0443). Improvements in IRLS total score (- 23.7 ± 11.2 vs -7.9 ± 11.0 placebo; p = 0.0002), RLS-6 severity scales during the night (p = 0.0010) and during the day (p = 0.0018), Clinical Global Impressions severity item (p = 0.0003), sleep quality (p = 0.0180), SF-A sleep quality (p = 0.0371), and QoL-RLS (p = 0.0247) were larger in patients treated with cabergoline compared with the placebo group.	Single-evening cabergoline is an efficacious and well-tolerated short-term therapy for sensorimotor symptoms of restless legs syndrome and associated sleep disturbances.	Patients were recruited in outpatient units of neurologic hospitals or in private neurologic sleep laboratories.
Oertel, 2007 (32) **Effect-RLS Study**	Primary RLS moderate to severe symptoms, male and female patients, 18 to 80 years of age, from 37 centers in 5 European countries (Austria, Germany, Norway, Sweden, and the Netherlands) were included in the study. (IRLS) of > 15. Their RLS symptoms had to be present for at least 2 to 3 days per week in the 3 months before study entry. Patients were barred from study entry if they were pregnant or breastfeeding women; were not using adequate contraception; were diabetic; or had significant renal, hepatic, gastrointestinal, pulmonary, or endocrine disorders. Also, patients with any other neurologic disease were excluded. Patients with sleep disorders unrelated to RLS, psychotic disorders, or mental disorders were excluded. In addition, patients with a history of substance abuse and those working on a shift schedule were not allowed to participate.	Moderate to severe; International RLS Study Group Rating Scale (IRLS) of > 15	345 (338) / Placebo:55.8 (SE 10.9); Pramipexole: 55.4 (SE 11.6) / Placebo:36M78F; Pramipexole 80M144F	Pramipexole was well tolerated throughout the study. In the course of the study, 7.0% of placebo-treated and 5.2% of pramipexole-treated patients discontinued prematurely. The most frequent reason for premature withdrawal was the occurrence of AEs in 4.3% (placebo) and 2.6% (pramipexole) of patients. Nausea and fatigue were slightly more frequent with pramipexole than with placebo.	The primary endpoint consisted of two assessments: the change from baseline in the IRLSSG Rating Scale and the proportion of patients with Clinical Global Impressions-Improvement (CGI-I) assessments of "much/very much improved" (CGI-I responders) at week 6. Secondary endpoints included PGI and IRLS responder rates. After 6 weeks, adjusted mean reductions (±SE) in IRLS score were 5.7 (± 0.9) for placebo (median dose 0.47 mg/day) and 12.3 (± 0.6) for pramipexole (median dose 0.35 mg/day; P<0.0001). CGI-I responder rates were 32.5% (placebo) and 62.9% (pramipexole) (P < 0.0001). For all secondary endpoints, pramipexole showed superior results.	Both assessments demonstrated significant improvement in RLS severity in pramipexole-treated patients compared with patients who had received placebo.Our results confirm the findings of Montplaisir and colleagues, who conducted the first randomized, doubleblind study with pramipexole in RLS.5,6	The low incidence of AEs observed with pramipexole is most likely related to the low doses needed to achieve efficacy in patients with RLS, compared with the dose range used in the treatment of Parkinson's disease of up to 4.5 mg/day.
Oertel, 2008 (107) **Rotigotine SP 709 Study Group**	Idiopathic RLS. Inclusions: 18-75 years of age; no previous treatment for RLS or, if pretreated, had responded previously, according to medical history information, levodopa therapy and/or treatment with a dopamine agonist; had a BMI 18-35 kg/m^2; and had an IRLS sum score of 15 or higher (=at least moderate RLS) at baseline. Exclusions: secondary RLS associated with, for example, end-stage renal disease or iron-deficiency anemia; a history of sleep disturbances if not caused by RLS; other concomitant neurological (e.g., symptoms or signs of polyneuropathy) or central nervous diseases or psychotic episodes; a medical history indicating intolerability to prior dopaminergic therapy (if pretreated). The following exclusion criteria were explicitly specified: QTc-interval in resting ECG >450 ms in males and >470 ms in females, history of symptomatic orthostatic hypotension within 28 days prior to screening, or a systolic blood pressure <105 mmHg at trial entry.	At least moderate (IRLS≥15 at baseline); stated "severe" in title	341 (333) / (mean age 58 ± 10 years, 67% females	The most frequent side effects were application site reactions and nausea and tended to be more frequent with higher doses. Overall, 46% of patients in the placebo group and 62% of patients in the rotigotine treatment groups reported one or more adverse events during the treatment period. More patients with the two highest rotigotine doses of 3 mg/24 h and 4 mg/24 h experienced an adverse event compared to the lower dosages and placebo. Application site reactions were the most frequent adverse event, showing an increasing rate of affected patients with increasing rotigotine dose.	Primary efficacy measure was the total score of the IRLS; in addition, the RLS-6 scales and the Clinical Global Impressions (CGI) were administered. The IRLS total score improved between baseline and end of the 6-week treatment period by -10.6 (0.5 mg/24 h rotigotine; patch area 2.5 cm^2), -15.1 (1 mg/24 h; 5 cm^2), -15.7 (2 mg/24 h; 10 cm^2), -17.5 (3 mg/24 h; 15 cm^2), and -14.8 (4 mg/24 h, 20 cm^2) as compared to placebo (-9.2). The hierarchical statistical test procedure demonstrated superiority of rotigotine over placebo for 4 mg/24 h, 3 mg/24 h, 2 mg/24 h, and 1 mg/24 h, with p-values of 0.0013, <0.0001, 0.0003, and 0.0004, respectively. Only the 0.5 mg/24 h dose was not different compared to placebo (p = 0.2338). The CGI and the RLS-6 severity items supported the efficacy of the rotigotine doses	This dose-finding trial identified the range for a maintenance dose of rotigotine from 1 mg/24 h to 3 mg/24 h. The lowest dose was ineffective and, with the highest dose, no additional benefit was observed.	
Oertel, 2008 (112) **Rotigotine SP 710 Study Group**	Idiopathic RLS. Of 310 patients who finished the controlled trial, 295 with a mean IRLS score of 27.8 ± 5.9 at baseline of SP709 were included. After the down tapering of trial medication in study SP709, patients were stratified into two groups: (1) those patients (85.4%) who improved in the IRLS total score between baseline and the end of study SP709 by at least 50% remained at first untreated but could enter study SP710 if their condition worsened during a treatment-free period of up to one-week (mean 6.4 ± 3.1 days); (2) the remaining 43 patients with no or only slight improvement could enter study SP710 immediately after the end of study 709.	Moderate to severe	295 (220) / mean age 58 ± 10 years (range 22–75 years) / 66% females)	The tolerability was described as "good" or "very good" by 80.3% of all patients. The most common adverse events were application site reactions (40.0%), which led to withdrawal in 13.2%. Further relatively frequent adverse events were nausea (9.5%) and fatigue (6.4%). Two drug-related serious adverse events, nausea and syncope, required hospitalization. Symptoms of augmentation were not reported by the patients.	For efficacy assessment the IRLS scale, the RLS-6 scales, the clinical global impressions (CGI) and the QoL-RLS questionnaire were administered. In addition, long-term tolerability and safety were assessed. The IRLS total score improved by -17.4 ± 9.9 points between baseline and end of Year 1 (p < 0.001). The other measures of severity, sleep satisfaction and quality of life supported the efficacy of rotigotine (p < 0.001 for pre-post-comparisons of all efficacy variables).	Rotigotine provided a stable, clinically relevant improvement in all efficacy measures throughout one year of maintenance therapy. The transdermal patch was safe and generally well tolerated by the majority of patients. Comparable to any transdermal therapy, application site reactions were the main treatment complication.	
Oertel, 2010 (111)	The study population was recruited at 11 clinical sites in fivewere included if they were either de novo subjects (defined as without any previous dopaminergic RLS treatment) or had a previous positive response to dopaminergic RLS treatment (however, previous rotigotine treatment led to exclusion). A PLM index (PLMI) score of P15 PLM/h time in bed (TIB) as documented by baseline polysomnography (PSG), a baseline sum score P15 points on the IRLSSG Severity Rating scale (IRLS [19], indicating at least moderate RLS), a score P4 at baseline for the Clinical Global Impressions (CGI [20]) item 1 assessment (severity of symptoms), and the ability to remove/apply patches correctly and consistently were additional inclusion criteria. European countries (Austria, Finland, Germany, Italy, and Spain). Male and female subjects aged 18–75 years. Subjects were excluded for secondary RLS (e.g., owing to renal insufficiency or iron deficiency), a history of sleep disturbances other than owing to RLS; other diseases excluded (see text)	Moderate to severe	Sixty-seven (46 rotigotine, 21 placebo) / 60.8 (9.4) for rotigotine and 56.3 (9.8) for placebo / 76% female for rotigotine and 70% female for placebo	Common drug-related adverse events for rotigotine and placebo included nausea (21.7%/4.8%), headache (17.4%/14.3%), application site reactions (17.4%/4.8%), and somnolence (10.9%/9.5%); most were mild to moderate in intensity.	Mean PLM index (PLMI; PLM/h time in bed) decreased more with rotigotine (50.9/h to 8.1/h) than with placebo (37.4/h to 27.1/h; adjusted treatment ratio 4.25 (95% CI [2.48, 7.28], p < 0.0001). PLM during sleep with arousal index (PLMSAI; 8.57/h to 2.47/h under rotigotine, 6.5/h to 4.95/h under placebo; adjusted treatment difference: 3.12 (95% CI [5.36, 0.88], p = 0.0072) also improved more under rotigotine. At end of maintenance, 39% of rotigotine subjects had PLMI levels <5/h and 26% showed no RLS symptoms (IRLS = 0), whereas no placebo subject met these criteria.	Rotigotine transdermal patch was efficacious and well tolerated in the short-term treatment of RLS motor symptoms and associated sleep disturbances.	
Ondo, 2005 (80)	Patients with refractory RLS who failed dopaminergics All RLS patients who have ever been prescribed methadone were identified through the RLS database at the Baylor College of Medicine Movement Disorders Clinic, and the treatment corroborated against retained Schedule II prescription records.	RLS refractory to dopaminergics; severity not stated	27 /32-81 (54.8)/14F 13M	2 dialysis RLS patients died while on methadone. Eight patients stopped methadone for the following reasons: adverse events (5), lack of efficacy (2), and logistical (1). Six of those eight stopped within the first month.Overall, after querying patients, 17 of 27 reported at least one adverse event on methadone, including constipation (11), fatigue (2), insomnia (1), sedation (1), rash (1), decreased libido (1), confusion (1), and hypertension (1).	In those continuing methadone, efficacy has been maintained over time and is rated as a 3, 4, or 5 in all patients (Table 1). Only a single patient has shown some evidence of dependency, and none have shown RLS augmentation. None of the patients who stopped methadone experienced any withdrawal symptoms.	All patients who remain on methadone report at least a 75% reduction in symptoms, and none have developed augmentation. Methadone should be considered in RLS patients with an unsatisfactory dopaminergic response.	
Ondo, 2010 (104)	Formal inclusion/exclusion criteria do not exist but all subjects had severe RLS (IRLS > 25) and were refractory to other multiple treatment modalities. Low serum iron indices were not an inclusion requirement.	Severe	25/21.1-73.7 (53.2±11.9)/7M 15F	Two subjects did not complete their entire infusion due to anaphylactic type symptoms but are included in the results; both had hypotension and urticaria. One resolved within 30 min and the other in approximately 90 min. Neither required hospitalization. Other adverse events were mild and included rash (2), headache (1), and nausea (1).	Overall, 2 subjects reported complete amelioration of all RLS symptoms, 11 reported marked improvement, 3 moderate improvement, 3 mild improvement, and 6 reported no improvement. For those with improvement, the duration of effect was highly variable, mean 15.8 ± 17.7 weeks, range 1–60 weeks. The time until clinical improvement was 4.5 ± 3.6 days. Thirteen subjects stopped or reduced their RLS medications after infusion. Twelve subjects had multiple infusions. Subsequent response varied and was both less and more robust in different patients. Reasons for not continuing infusions (13 total subjects) include relative lack of efficacy (9), not needed due to RLS improvement (4), allergic reaction (2) and high (>1000 ng/ml) serum ferritin (2). Several subjects had more than one reason for not continuing.	Iron dextran can dramatically improve refractory RLS but results are inconsistent and not predicted by patient demographics. Although burdened by a higher rate of anaphylactic reactions, iron dextran may be superior to other IV iron preparations.	
Partinen, 2006 (33) **PRELUDE Study**	Moderate to severe RLS. All participants were required to have PLMS at least five times per hour, as documented by baseline polysomnography, and also weekly RLS symptoms that had disrupted sleep within the previous 3 months. Females of childbearing potential and males were required to use adequate contraception and females who were pregnant or breast-feeding were excluded. Potential participants were also excluded for medical contraindications to use of pramipexole, for medical conditions or prescriptions that might influence disease course (including but not limited to diabetes mellitus, anemia, renal or hepatic disease), and for comorbid conditions that may cause or complicate symptoms of RLS.	Moderate to severe	109 (107) / 56.2 years [standard deviation (SD)=10.9] (27-76) / 28M 79F	Pramipexole was well tolerated and did not produce somnolence at any dose. The overall incidence of AEs was similar between placebo and pramipexole total (77.3 vs. 74.7%). The most frequently reported AEs (>5%) more often reported in the combined pramipexole groups than in the placebo group were nausea (14.9 vs. 4.5%) and nasopharyngitis (6.9 vs. 0.0%). Conversely, fatigue (22.7 vs. 18.4%) and headache (31.8 vs. 19.5%) were reported more frequently in the placebo group than in the combined pramipexole groups. Aggravation of RLS was observed in four patients (3.7%): one at 0.125 mg, two at 0.25 mg, and one at 0.50 mg. Somnolence was reported by three patients (2.8%), all at the 0.125 mg level.	Primary endpoint: PLMI. Secondary assessments: additional PSG measures, subjective ratings IRLS, on clinician-rated scales (CGI), patient-rated (patient global impression (PGI)) scales, quality of sleep and daytime well-being, as evaluated by self-reported ratings of sleep quality, daytime somnolence, and quality of life (QOL). In each pramipexole dose group, the PLMI decreased significantly, compared with placebo (adjusted mean difference in log-transformed data: 0.125 mg,-1.54; 0.25 mg,-1.93; 0.50 mg,-1.89; and 0.75 mg,-1.52; P<0.0001). At all doses, IRLS scores were also significantly reduced, with the greatest adjusted mean reduction in the 0.50 mg group (-17.01). At all but the lowest pramipexole dose, the percentage of responders (≥50% reduction of IRLS score) was substantially higher than for placebo (61.9–77.3, vs 33.3%). In the pramipexole groups, 50.0–77.3% of patients rated their condition as 'much better' or 'very much better', compared with 38.1% of patients in the placebo group (P=0.0139 for the 0.50 mg dose). Clinical global impressions (CGI) scale ratings of 'much improved' or 'very much improved' were given to 61.9–86.4% of patients in the pramipexole groups, compared with 42.9% in the placebo group (P<0.05 for the 0.25, 0.50, and 0.75 mg groups).	Pramipexole is effective and safe in the treatment of both objective and subjective facets of RLS.	

Evidence Table
The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Inclusion/ Exclusion criteria	RLS Severity	Sample size (completed) / mean age (age range or standard deviation) / gender of subjects	Adverse effects	Outcome measures / results	Conclusions	Comments
Partinen, 2008 (39)	Patients with a confident diagnosis of idiopathic RLS, a PLM index (PLMI) of ≥5 per hour, an International RLS Study Group Rating Scale (IRLS) severity score of >15, and a weekly presence of sleep-disrupting RLS symptoms throughout the previous three - months.Patients were excluded for inadequate contraception, pregnancy, or breast-feeding, for having contraindications to pramipexole; for medication or medical disorders that might affect RLS (including, but not limited to, diabetes, anemia, and renal or hepatic disease); for comorbid conditions that might have caused RLS; for current RLS treatment (within the previous week); and for recent participation in an investigational drug study (within the previous 60 days).	Moderate to severe (PLMI≥5/h and IRLS>15)	141 recruited; 109 randomized; 107 completed /18-80/79F 28M	Of the 107 patients who entered the open-label phase, 90 (84.1%) reported AEs. The majority were mild (84 patients) or moderate (22 patients) in severity.The most frequently reported drug-related AEs were fatigue (10.3%), nausea (6.5%), and peripheral edema (5.6%). All other drug-related AEs had a frequency of <5%.	Efficacy evaluations included the International RLS Study Group Rating Scale (IRLS), Patient Global Impression (PGI) scale, Clinical Global Impressions-Improvement (CGI-I) scale, Epworth Sleepiness Scale (ESS), and Short Form-36 (SF-36) Health Survey. Subjective Sleep Quality was assessed by patient ratings of sleep and morning tiredness. The mean reduction in IRLS score was 73.5% (P < 0.05). The IRLS responder rate, defined by score reduction of P50%, was 81.3%. On the PGI scale, 89.7% of patients rated themselves as "very much" or "much" better. By CGI-I assessment, 94.8% of patients were considered either "very much" or "much" improved. Mean ESS score showed a modest but statistically significant reduction (P < 0.05) within the normal range, indicating that long-term pramipexole did not increase daytime sleepiness. On the SF-36 all 8 domains showed improvement, 5 of them statistically significant (P < 0.05) and 4 of these 5 (role-physical, bodily pain, vitality, and role-emotional) by >10 points on a 100-point scale. Subjective Sleep Quality also improved.	Pramipexole is well tolerated and effective for long-term treatment of RLS.	
Pellecchia, 2004 (137)	Patients on chronic hemodialysis. Patients with clinically significant orthostatic hypotension or an unstable medical condition including serious cardiovascular, pulmonary, hepatic, or psychiatric disease and with concurrent or past diagnosis of malignant melanoma were excluded from the study.	Moderate according to baseline data	11 (10) / Mean (± SD) age was 56.2 (± 8.7) years / 7M 4F	Under treatment with levodopa SR, 1 patient presented severe vomiting, leading to study discontinuation. No adverse event was observed during ropinirole treatment.	Patients rated the severity of RLS by means of a 6-item questionnaire developed by the International Restless Legs Study Group (6-item IRLS), by the Clinical Global Impression (CGI) scale, and by sleep diaries. A 33.5% improvement (from 16.7 ± 3.2 to 11.1 ± 4; P < 0.001) of the 6-item IRLS scores during levodopa SR treatment and a 73.5% improvement (from 16.6 ± 2.8 to 4.4 ± 3.8; P < 0.001) during ropinirole treatment. Ropinirole was superior to levodopa SR in reducing 6-item IRLS scores (P < 0.001) and in increasing sleep time (P < 0.001). The patient CGI scale showed a significant difference favoring ropinirole (P < 0.01). There was no significant carryover or period effect for any outcome measure. Four patients reported a complete reversion of RLS symptoms during ropinirole treatment at doses ranging from 0.25–2 mg/d.	These results suggest that ropinirole is more effective than levodopa SR in the treatment of RLS in patients on chronic hemodialysis.	
Polo, 2007 (60)	RLS patients with PLM. Male and female patients aged 20- 75 years; PLMs > 5 per hour (TST or TIB) in either leg on both screening nights. Exclusions: RLS was judged to be associated with a known condition such as diabetes, hypothyroidism, uremia, or polyneuropathy, or if they worked night shifts; clinically significant deficiency in iron, vitamin B12, magnesium, or erythrocyte folate; clinically significant abnormalities in serum thyroid stimulating hormone or free thyroxine values; or any clinically significant finding on laboratory or physical examinations, including electrocardiogram (ECG), or apnea/hypopnea index higher than 10 per hour during the first PSG screening night; use of dopaminergic or psychotropic treatments within the month before screening or had previously participated in a clinical study using entacapone. Any condition that could interfere with the efficacy assessments or represent a safety hazard to the patients (including drug or alcohol abuse and excessive nicotine intake) resulted in exclusion.	Not stated	28 / The age of the study population ranged from 27 to 68 years, with a mean age of 51.2 (9.9) years / 10M 18F	All formulations were well tolerated. In this setting, levodopa preparations such as Stalevo (LCE) are likely to be good options because there would be no need for dose titration to alleviate side effects such as headache and nausea, which is the case with dopamine agonists. The present study supports this view because single doses of LCE containing up to 150 mg of levodopa were effective and at the same time well tolerated, lacking typical dopaminergic sideeffects such as nausea.	Periodic limb movements per hour (PLM/h) during total sleep time and PLM during total time in bed were the primary and secondary variables, respectively. Polysomnography recordings were performed on 2 nights at screening and on 1 night after each treatment, beginning at bedtime and continuing for at least 7 hours. Mean PLM/h during total sleep time after Stalevo 50 (12.6/h, P < 0.05), LCE100, LCE150, and LC100 (6.4/h, 3.5/h and 9.5/h, respectively; P <0.01) were significantly reduced compared with placebo (25.7/h). Improvement was also observed in PLM/h during total time in bed for all treatments (P <0.01) and a significant dose response observed between LCE doses (P < 0.05). Compared with LC100, LCE100 and LCE150 reduced PLMs during the second half (P = 0.06 and P < 0.001, respectively) or during the last 3 early morning hours (hours 5-7 from the start of recording) of the night (P < 0.05 and P < 0.01, respectively).	Single doses of LCE tablets decreased PLMs in a dose-related manner in RLS patients. Prolonged effects of levodopa on PLMs suggest that, compared with standard levodopa, this new levodopa formulation provides longer symptom control throughout the night in patients with previously untreated RLS. In conclusion, these results suggest that the therapeutic potential of conventional LC therapy in RLS can be increased with LCE. This conclusion is based on the observation that the PLM frequency decreases and remains decreased over the whole night with LCE100 and LCE150.	Only LCE150 is better than LC100 for PLM/h TST
Rottach, 2008 (127)	INCLUSION CRITERIA • Patients over 18 years of age with diagnosis groups F3 and F4 (ICD10) • Initial treatment with an "modern" AD EXCLUSION CRITERIA • Treatment-requiring RLS • Comedication with drugs effective in RLS (L-dopa, carbamazepine, gabapentin, dopamine agonists, opiates).	Varied	327 included; 271 completed / not stated / 67% Female	N/A	In 9% of patients, RLS was recorded as a side effect related to the administration of AD. The frequency of this side effect varied among the drugs. The problem is most pronounced with mirtazapine provoking or deteriorating RLS in 28% of patients. By contrast, no case occurred during use of reboxetine. As for the other AD, the rate of newly occurred and deteriorated RLS, ranged from 5% to 10%. Typically, RLS occurred during the initial days of treatment. In 12 of 24 patients who developed RLS, the AD had to be switched or discontinued for that reason. In the other 12 patients, the side effect was tolerable and did not affect further treatment. In some of the affected patients, RLS abated in the further course of treatment. Another result of the study is that ADinduced RLS usually occurs within the first days of treatment rendering the problem more manageable. It might suffice to ask the patient for RLS symptoms at the first visit following onset of treatment. If no symptoms have occurred by then, RLS is unlikely to appear in the further course of treatment.	Antidepressant-induced RLS definitely exists – with considerable differences observed between the various substances. While pure SSRIs and SNRIs carry an average risk of about 5% for triggering RLS, reboxetine does not seem to induce this syndrome. By contrast, mirtazapine is clearly the most problematic substance: it caused or worsened RLS in almost 30% of the patients surveyed. Due to the fact that the mirtazapine patients in this study were on average older than the other patients, this rate may be somewhat overestimated due to an additional age effect.	If the symptoms are not too pronounced, the medication can be maintained with a chance of abatement of RLS in the short term. If RLS discomfort is intolerable, the patient may be switched to another AD, because the probability that RLS recurs with the new drug is not too high. The safest way should be a switch to reboxetine as it does not seem to induce RLS.
Sakkas, 2008 (139)	Clinically stable patients on long-term dialysis. Entry criteria for the study were RLS diagnosis and receipt of chronic HD for 6 months or more with adequate dialysis delivery (KT/V >1). Patients were excluded whether they had reasons for being in a catabolic state (including malignancies, HIV, opportunistic infections, infections that required intravenous antibiotics, etc.), within 3 months before enrollment. Patients with polyneuropathy or vascular disease of lower extremities or with ankle to brachial index (ABI) < 0.95 were also excluded.	Moderate to very severe according to baseline data	14 / (four female, mean age 59 ± 16 years)	Not stated	Primary aim was to compare the International RLS (IRLS) study group rating scale, functional ability, and quality of life in baseline and the end of the 16 weeks. Exercise training reduced IRLS score by 42% (p= 0.02) [26 (6) to 15 (9)]. Furthermore, it significantly improved indices of functional ability (p= 0.02), exercise capacity (p= 0.01), quality of life (p =0.03), and sleep quality (p= 0.01). In the Con-group no changes were observed [IRLS, baseline 24 (8), after 25(5)].	In conclusion, aerobic exercise training is safe and efficacious in reducing RLS symptoms and improving quality of life in patients with RLS on HD.	Significant difference in age between Ex-group and Con-group, p=0.01. Ex-group was 48 (14), Con-group was 70 (11). The exercise group (Ex-group) was younger with higher levels of LBM compared with the control group (Con-group) (p < 0.05). We currently cannot exclude the possibility of a placebo effect in our study
Saletu, 2001 (121)	RLS and PLMD of either sex. Excluded from the study were: patients with evidence of a medical or psychiatric disorder that might account for the primary complaint; patients with signs of secondary RLS; patients with other pathophysiologies such as obstructive sleep apnea or narcolepsy; pregnant or lactating women; women in the child-bearing period who were not applying adequate contraceptive methods; patients with a history of drug abuse or dependency, including alcohol; patients requiring psychoactive medication or any other drug that might interfere with the study assessments; patients who were unable or unwilling to comply with the protocol; patients who worked at night.	In the RLS group, 2 patients were considered mild, 5 moderate and 3 severe cases. In the PLMD group, there were 7 mild, 5 moderate, and 4 severe cases.	10 RLS (five males, five females) in the age range of 34–68 years (mean 52.9±8.7 years) / and 16 PLMD (seven males, nine females) in the age range of 25–68 years (mean 53.4±12.4 years)	Not stated	Objective and subjective sleep and awakening quality, utilizing PSG and psychometry (Grunberger Alphabetical Cancellation Test for quantification of attention, concentration, and attention variability; the Numerical Memory Test; the Grunberger Fine Motor Activity Test for changes in psychomotor activity and drive. Descriptive data analysis demonstrated at the confirmatory level concerning three target variables that — as compared with placebo — clonazepam significantly improved objective sleep efficiency and subjective sleep quality in both patient groups, but failed to reduce the index PLM/h of sleep. At the descriptive level, in PLMD clonazepam improved PLM during time in bed, REM and wakefulness and showed more significant changes in various sleep and awakening measures than in RLS patients, though there were no significant inter-group differences.In the PLMD group, significant decreases occurred in PLM/h TIB, PLM/h REM, as well as in PLM during wake-time after 1 mg clonazepam as compared with placebo, whereas in the RLS group there were no significant changes concerning the mentioned variables	In both PLMD and RLS clonazepam exhibited acute therapeutic efficacy regarding insomnia, which is quite different from the mode of action of dopamine agonists.	According to the ICSD criteria on PLM severity, in the RLS group two patients were considered mild, five moderate and three severe cases. In the PLMD group, there were seven mild, five moderate and four severe cases.
Saletu, 2002 (41)	Inclusion criteria called for patients of either sex, and showing stable symptoms during the 2 weeks before the study. The polysomnographic screening night had to reveal an abnormal PLM index (more than five PLM per hour of sleep). Exclusion criteria were evidence of a medical or psychiatric disorder that might account for the primary complaint, signs of secondary RLS or other pathophysiologies such as obstructive sleep apnea or narcolepsy. Furthermore the following were excluded: pregnant or lactating women; women in the child-bearing period who were not applying adequate contraceptive methods; patients with a history of drug abuse or dependency including alcohol; patients requiring psychoactive medication or any other drug that might interfere with the study assessments; patients who were unable or unwilling to comply with the protocol; patients who worked at night.	Not stated	16 (11 Part 1, 10 Part 2) / (35- 74 years) mean 54.2±13.6 years / 8M 3F	All 11 patients completed the study. Minor side-effects possibly related to the therapy were nausea (n=2), headache (n=1) and vertigo (n=2).	In 3 nights (pre-treatment, placebo and drug night), objective sleep quality was determined by PSG, subjective sleep and awakening quality by rating scales, objective awakening quality by psychometry. Clinical follow-up consisted of completion of theRLSSG Scale, Zung Depression (SDS) and Anxiety (SAS) Scale, Quality of Life Index, Pittsburgh Sleep Quality Index and Epworth Sleepiness Scale. Concerning acute effects, an omnibus significance test for PSG variables demonstrated a global difference between placebo and pramipexole, but none between pre-treatment and placebo. Pramipexole 0.27 mg significantly decreased the target variable periodic leg movements (PLM)/h of sleep by 78% as well as all other RLS/PLM variables and improved objective sleep efficiency by 19% and subjective sleep quality as compared with placebo. In sleep architecture, sleep stages S1 and S2 and stage shifts increased, while slow-wave sleep and SREM decreased. After 4 weeks of therapy, the total scores of the IRLSSG questionnaire, sleep quality and daytime sleepiness, depression and quality of life also improved.	Thus, acute pramipexole markedly reduced PLM measures and slightly improved objective and subjective sleep quality. Follow-up ratings showed a moderate improvement of RLS and sleep quality, and to a lesser extent of daytime sleepiness, depression and quality of life. The psychopathological findings as well as acute sleep architecture changes are reminiscent of those seen after activating antidepressants.	
Saletu, 2003 (58)	Patients were recruited from outpatient clinics for sleep disorders of the Dpt of Psychiatry, U of Vienna and the Dpt of Neurology, U of Innsbruck. Inclusion criteria called for patients of either sex, satisfying the classification criteria for RLS (780.52–5), as determined by the ICSD 1997 and IRLSSG and showing stable symptoms during the two weeks before the study. Abnormal PLM index (> five PLM per hour of sleep) during PSG. Exclusions: patients with evidence of a medical or psychiatric disorder that might account for the primary complaint (e.g. polyneuropathy); patients with signs of secondary RLS (e.g. iron deficiency); patients with other pathophysiologies such as OSA or narcolepsy; pregnant or lactating women; women in the child-bearing period who were not applying adequate contraceptive methods; patients with a history of drug abuse or dependency including alcohol; patients requiring psychoactive medication or any other drug that might interfere with the study assessments; patients who were unable or unwilling to comply with the protocol; patients who worked at night.	Not stated	21 for acute (18 for 4 week f/u) / mean 63 ± 14.3 years (37-81) / 8M 13F	Two patients discontinued the dopaminergic treatment because of lack of therapeutic efficacy in regard to sleep quality. One of these two complained of tachycardia and stomachache. One patient reported "augmentation". Minor side effects possibly related to the combination therapy were nausea (n = 3), stomachache (n = 1), tachycardia (n = 1), dry mouth (n= 3), headache (n = 1) and nycturia (n = 2). There were no adverse drug reactions on placebo.	Objective sleep quality was determined by PSG in 3 subsequent nights (adaptation/screening, placebo and drug night), subjective sleep and awakening quality was evaluated by rating scales, objective awakening quality by psychometric tests. Clinical follow-up consisted of daily ratings of subjective sleep and awakening quality (SSA) and VAS for RLS symptomatology ratings, completion of the RLS (IRLSSG) Scale weekly and the Zung Depression (SDS) and Anxiety (SAS) Scale, Quality of Life Index, Pittsburgh Sleep Quality Index and Epworth Sleepiness Scale before and after therapy. Acute L-dopa/benserazide significantly (p< 0.001) and markedly (75%) decreased the target variable PLM/h of sleep as well as all other RLS/PLM variables, but failed to improve objective sleep efficiency and subjective sleep quality in comparison to placebo. After 4 weeks of therapy, however, subjective sleep and awakening quality also improved significantly.	While RLS/PLM measures showed an immediate significant and marked response to the combination therapy subjective sleep quality only improved after chronic treatment.	

Evidence Table
The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Inclusion/ Exclusion criteria	RLS Severity	Sample size (completed) / mean age (age range or standard deviation) / gender of subjects	Adverse effects	Outcome measures / results	Conclusions	Comments
Shinno, 2010 (122)	Patientswere eligible if (i) theywere aged≥20 years, (ii) clonazepam had been prescribed (≤2.0 mg/day), (iii) daily doses of clonazepamdid not change for more than 4 weeks, and no other drugs were prescribed for RLS. Patients were excluded for pregnancy or breast-feeding; for having contraindications to pramipexole; for comorbidity with other sleep disorders. Patientswere also excluded fromthis study if the causes of RLS were pregnancy, renal failure, artificial dialysis, or drugs such as neuroleptics and antidepressants	None/Mild: 6 before switch/16 after Moderate: 9 before switch/ 7 after Severe: 8 before switch/ 1 after Very Severe: 1 before switch/ 0 after (IRLS)	26 (24)/44-86 (69.2 ± 11.0)/14M 12F	Of the 4 patients who exhibited adverse events, two patients required the discontinuation of pramipexole due to mild nausea (daily dose of pramipexole: 0.25 mg/day) or diarrhea (daily dose of pramipexole: 0.25 mg/day), which lasted for 1 day and 3 days,respectively. The others transiently complained of somnolence (daily dose of pramipexole: 0.25 mg/day) and sensation of oppression in the legs (daily dose of pramipexole: 0.125 mg/day), but continued pramipexole treatment.	Conversion from clonazepam to pramipexole resulted in significant reductions of IRLS (16.3±8.7 to 9.1±6.3) and ESS (6.5±4.2 to 4.4±3.2). The mean CGI-S scores at baseline and after conversion were 3.9±1.3 and 2.7±0.9, respectively	Statistical analysis demonstrated a 4:1 conversion for clonazepam to pramipexole. When switchover from clonazepam to pramipexole is done, this conversion ratio may be helpful to determine the initial dose of pramipexole for treating RLS.	
Silber, 2003 (43)	A minimum of 4 months of follow-up data available or patient known to have discontinued pramipexole within 4 months of initiation.	Not stated	60 / 57.7 years (range, 25-82 years) / 36F 24 M	40 percent experienced mild side effects, most commonly insomnia, nausea or dyspepsia, and dizziness. Only 5% experienced sleepiness, and none experienced sleep attacks while driving. Augmentation developed in 33%, most in the first year and all by 30 months. Augmentation was not predictable by prior augmentation with other dopaminergic agents. Only 1 patient discontinued pramipexole because of augmentation.	Efficacy was judged from the charts by the reviewing physician and graded as completely effective (no residual RLS), partially effective (improvement in RLS, but some RLS still present), and ineffective (no improvement in RLS). Sleepiness was determined by patient report on follow-up visits. Epworth Sleepiness Scales (ESS) were available for some patients but not systematically recorded Pramipexole was completely effective in controlling RLS in 67%, partially effective in 27%, and ineffective in 7% of patients. Eleven patients (18%) discontinued pramipexole after less than 4 months; the remainder were followed for a mean of 27.2 months, during which only 4 others stopped the drug.	Pramipexole was effective for RLS with continued response with time. Modest escalations in dose occurred, partly due to additional doses prescribed for augmentation. Side effects were common, but generally mild and tolerated. Sleepiness while driving was not a problem. Augmentation occurred in 33% of patients but was treatable with increased doses earlier in the day.	
Sloand, 2004 (136)	Patients with ESRD. Patients were excluded if they were of childbearing potential or had severe liver disease, polycythemia, evidence for hemochromatosis, a history of 10 or more blood transfusions during the 2 years before the study, a history of hypersensitivity to IV iron, receipt of any IV iron within 1 month of enrollment, weight less than 50 kg, urea reduction ratio less than 65% (unless kinetic modeling using Kt/V was > 1.2), a change in dialysis prescription within 3 months of entry, fistula recirculation greater than 12%, or active inflammatory or rheumatologic disease.	Not stated	25 / 58 (48-65) treatment; 53 (41-68) placebo / 55% M treatment; 71% M placebo	No differences in adverse events were noted between groups. No patient experienced immediate or shortterm adverse effects from iron dextran.	Patient demographic data were collected, and blood chemistry tests, liver function studies, serum iron levels, ferritin levels, and total iron-binding capacity were obtained at baseline and 1, 2, and 4 weeks postinfusion. RLS symptoms were assessed by a rating scale at the same intervals. A 3-question assessment tool was developed with the assistance of the Movement and Inherited Neurological Disorders Unit of the University of Rochester. The questionnaire was developed to determine the severity of RLS symptoms using a 0-to-10 rating scale. Questions posed included the following. (1) Over the past 2 days, have you had an unpleasant restless feeling in your legs at night that is relieved by moving the legs? (Rate as 0 never, 1 rarely, 2 occasionally, 3 often, 4 every night.) (2) How distressing is the sensation? (0 no distress, 1 mild, 2 moderate, 3 severe.) (3) How long do these sensations last? (0 no time or a few seconds, 1 30 minutes, 2 30 minutes to 1 hour, 3 1 hour.) Although no change in symptoms were seen in the placebo-treated group, significant improvement in RLS symptom scores in response to iron dextran was seen 1 week after infusion (-2; interquartile range [IQR],- 6 to -1; P =0.03, Wilcoxon's rank sums), but was greatest at 2 weeks (-3; IQR,-5 to -2 compared with -1 to 0; P= 0.01). Salutary effects of iron persisted at 4 weeks, but were no longer statistically significant. The significant increase in serum ferritin levels and iron saturation observed in theiron dextran–treated group was not seen in the placebo-treated group.	High-dose iron dextran infusion is associated with a significant, but transient, reduction in symptoms of RLS in patients with ESRD.	
Sommer, 2007 (149)	16 patients with secondary RLS, in most of them due to neuropathy, seven of them with and nine without neuropathic pain, and to three patients with idiopathic RLS.	Not stated	19 (16) / 63.2 (SD=6.4) / 9M 10M	Three patients discontinued pregabalin because of side effects (rash, fatigue, loss of efficacy). Sixteen patients tolerated pregabalin well, including two of the three with idiopathic RLS, with only minor side effects, mostly fatigue and dizziness.	Patients were asked to score their relief from core RLS symptoms due to medication at every visit with a score of 1 indicating 'very good' symptom control, 2 for 'good ', 3 for 'satisfactory' , 4 for 'poor' and 5 for 'very poor' . All the 16 patients self-rated a satisfactory or good alleviation of RLS symptoms and maintained pregabalin, five with add-on medication, on a mean daily dose of 305 mg (SD=185 mg), and with a mean duration of 217 (standard deviation, 183) days.	These data propose pregabalin as a new option in the treatment of secondary RLS for patients with neuropathic pain, which should be further investigated with randomized, placebo-controlled trials.	
Stiasny-Kolster, 2004 (64)	Patients with moderate to severe idiopathic RLS with or without augmentation. Patients aged 18 to 75 years were eligible to participate in the study if they had RLS severity at night of ≥4 on an 11-point RLS-6 rating scale ranging from 0 = symptoms not present to 10 = very strong. Patients were excluded from the study if there was evidence of a disease frequently considered to be associated with RLS symptoms, e.g., uremia, iron deficiency, and rheumatoid arthritis. Additional exclusion criteria were idiopathic Parkinson's syndrome, insulin-dependent diabetes mellitus, polyneuropathy, liver disease, history of sleep apnea, malignancy, pleural effusions or fibrosis, and established or suspected hypersensitivity to ergot alkaloids. In addition, women were excluded if they were pregnant, at risk for pregnancy during the study, or lactating.	RLS severity at night of 4 on an 11-point RLS-6 rating scale ranging from 0 = symptoms not present to 10 = very strong (i.e., only patients with moderate to severe symptoms were included).	84 for efficacy and 85 for safety; 66 completed long-term trial / 56.1 ± 10 / 69.7% F	Table 1 has specifics. The most frequent AEs: nausea, constipation, headache, dizziness, fatigue, drowsiness, "augmentation". One serious AE occurred (hallucinatory psychosis) About one third of all patients had a drug-related AE during the titration period II (31.6% of 85) or the long-term period III (36.4% of 66) period. During long-term treatment, 6 of 66 treated patients were affected (n =2) or possibly affected (n =4) by mild augmentation. Under CAB therapy up to 1 year, 11 of 85 (13%) patients discontinued treatment due to a drug-related adverse event.	Severity of RLS-6 scale symptoms during the night (the primary endpoint) was markedly improved by all CAB doses compared to placebo (placebo:-1.4 ± 3.1, 0.5 mg CAB:-4.2 ± 3.0 [p = 0.0082], 1.0 mg CAB:-4.0 ± 2.9 [p= 0.0040], 2.0 mg CAB: -4.8 ± 3.7 [p = 0.0026]). Similar results were found for the RLS severity at bedtime and during the day, IRLS, and satisfaction with sleep. A stable, clinically relevant improvement was achieved in all efficacy measures (severity during the night: change between last assessment and baseline: -5.6 ± 2.5, rate of remission: 71.2%) throughout 1 year with a mean CAB dose of 2.2 mg per day.	Cabergoline is an efficacious and well-tolerated option for the treatment of restless legs symptoms during the night and the day.	Patients were recruited in outpatient units of neurologic hospitals or by neurologists in private practices. The average daily cabergoline dose at the end of the long-term period (III) was 2.2 ± 1.1 mg (median dose: 2.0 mg).
Stiasny-Kolster, 2004 (42)	Primary RLS; patients who were being insufficiently treated with levodopa or for whom pramipexole was primarily being considered because of the severity of the RLS symptoms.	Moderate to severe	17 / mean age 61.9 ± 9.4, range 48–79 years / 12F 5M	Although Patient 6 was free of RLS symptoms while receiving 0.250 mg pramipexole, sleep disturbances aggravated, in particular when attempting to fall asleep. We advised her to take pramipexole earlier in the evening (at about 17.00 h), which improved her sleep considerably. In another patient (Patient 15), who was successfully medicated for cardiac arrythmias before entering the study, arrhythmias subjectively reappeared under 0.250 mg pramipexole. After reduction to 0.125 mg, a dose which still controlled the patient's RLS symptoms, the arrhythmias disappeared and were not detectable on ECG.	Significant improvement of subjective RLS symptoms as rated by the International RLS Study Group Severity Scale (IRLS scores: 29.8 ± 4.7 baseline vs. 7.3 ± 5.9 endpoint; p = 0.0001). Polysomnographic recordings showed a significant improvement of the periodic leg movements (PLM) index, PLM sleep arousal index, sleep-onset latency, total sleep time and sleep efficiency efficiency. All patients who had developed a worsening of RLS symptoms under levodopa recovered from daytime symptoms after their medication was switched to pramipexole.	Pramipexole has proven a suitable alternative in patients with moderate to severe RLS, particularly when their therapy has to be switched to a dopamine agonist.	Since pramipexole was well tolerated, an ideal dosage to control RLS symptoms could be reached rapidly.
Stiasny-Kolster, 2004 (108)	Patients with moderate-to-severe idiopathic RLS, including daytime symptoms. Inclusion: Patients 18-75 years of age, had a ≥ 10 in the IRLS severity scale (at least "moderate RLS"), a minimum score of 3 in the RLS-6 scale "severity of RLS during the day when at rest," and had responded previously to levodopa if they were pretreated. Exclusions: any form of secondary RLS, history of sleep disturbances if not caused by RLS, concomitant neurological or central nervous diseases, or psychotic episodes.	Moderate to severe	63 (62) / mean age, 58 ± 9 years; 64% women	No serious adverse event occurred in this study.The most frequently reported AEs were mild, transient application site reactions, which were reported with similar frequency in all treatment groups. Those were well tolerated and required no changes in dose. Headache was also a frequently reported adverse reaction to treatment. Two of all drugrelated AEs were of severe intensity: 1 patient of the 2.25-mg rotigotine group suffered from headache, and 1 patient of the 4.5-mg group from fatigue. Overall, treatment- related AEs were slightly more frequent in the two higher rotigotine dose groups than in the placebo or 1.125-mg rotigotine groups.	The primary efficacy measure was the total score on the IRLS Scale. Additionally, the RLS-6 scale, the Clinical Global Impressions (CGI), and a sleep diary were used. RLS severity improved related to dose by 10.5 (1.125 mg RTG/d; P= 0.41), 12.3 (2.25 mg RTG/d; P=0.18), and 15.7 points (4.5 mg RTG/d; P < 0.01) on the IRLS compared to placebo (8 points). According to the RLS-6 scales, daytime symptoms significantly improved with all rotigotine doses. The CGI items supported the favorable efficacy of the 4.5-mg dose. Skin tolerability of the patches and systemic side effects were similar between rotigotine and placebo.	This pilot study suggests that continuous delivery of rotigotine by means of a patch may provide an effective and well-tolerated treatment of RLS symptoms both during night and day.	
Thorp, 2001 (134)	Hemodialysis patients from Veterens population. Patients eligible for the treatment phase of the study had the presence of all four characteristics, at least two of which were constantly present (resulting in a minimum score of 6), and no evidence of other cause on neurological examination.	Not stated	16 (13) / 64 (51-74) / 15M 1F	2 patients dropped out due to lethargy. We note that the primary symptom from patients on the medication was lethargy, although it was only limiting in two patients.	A questionnaire regarding symptoms of RLS. The criteria developed by the International RLS Study Group served as a guideline. The cumulative result of each questionnaire was recorded as both a parametric (from 0 to 8) and nonparametric value (RLS or no RLS). The mean score before the study was 6.9 ± 0.7. After placebo administration (before or after crossover), the mean score among patients who completed the study was 5.8 ± 2.3. Only two patients' scores were less than 6. After gabapentin administration (before or after crossover), the mean score among patients who completed the study was 3.0 ± 2.2. Two patients had scores of 6 or greater. 11 patients responded to gabapentin but not placebo, p<0.01. One pt responded to both, and 1 to placebo but not gabapentin	Gabapentin is an effective treatment for RLS in hemodialysis patients.	
Trenkwalder, 2003 (59)	For a patient's inclusion in the extension trial, a positive treatment response without relevant tolerability problems in at least one crossover period was postulated.	Not stated	23 (10 completed 12 months) / 56 ± 10 (31–72) / 7M 16F	Of 13 dropouts, 8 patients discontinued therapy because of worsening RLS during the day (probably augmentation, 8 patients), lack of efficacy (1 patient, maximum daily levodopa dose of 800 mg per day, which was chosen by the patient herself without informing the investigator), diarrhea (1 patient), withdrawal of consent (n = 2), lost to follow-up (n = 1). Two serious adverse events were observed in this trial: sick sinus syndrome with persistent bradycardia (1 patient), not related to levodopa therapy, as well as persistent diarrhea (1 patient), related to levodopa therapy. Seventy-three adverse events were documented, with worsening of RLS in 13 patients, dry mouth (7 patients), and itching (5 patients) as the most frequent adverse events.	Efficacy was documented using patient's rating scales, sleep diaries, and investigator's global ratings with the Clinical Global Impressions (CGI). quality of sleep improved (3.5 ± 1.9, 7-point scale), sleep latency was shortened (-131 ± 152 minutes), and total sleep time lengthened (190 ± 136 minutes). Severity of RLS at time of falling asleep (-6.5 ± 3.4, 11-point scale) and during the night (-6.0 ± 3.5) was markedly lower at the end of the extension but severity of RLS during the day (1.9 ± 5.0) slightly increased.	This trial shows that long-term treatment with the combination of RR and SR levodopa/benserazide in RLS patients with late-night problems was efficacious and not limited by tolerability problems in 40% of patients, whereas in the majority of patients, aggravating daytime problems required termination of the levodopa therapy within the 1-year treatment period. Therefore, one major recommendation derived from the data in this extension period may be that patients should not be allowed to increase the levodopa dosage ad libitum, e.g., beyond 400 mg levodopa/day to avoid an increased risk of augmentation or rebound during day time. One should, therefore, switch to other dopaminergic therapies in the event that higher levodopa doses than 400 mg are needed.	There are still no double-blind, placebo or activecontrolled, long-term studies showing that higher doses of levodopa are associated with a higher prevalence of augmentation, although such a relationship is acknowledged mainly from clinical experience.

Evidence Table
The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Inclusion/ Exclusion criteria	RLS Severity	Sample size (completed) / mean age (age range or standard deviation) / gender of subjects	Adverse effects	Outcome measures / results	Conclusions	Comments
Trenkwalder, 2004 (62)	Idiopathic RLS. ≥18 years. 17 centers in Europe. Inclusion: sleep disturbance with symptoms or treatment required for at least 3 months before study entry; PLMS AI >5/h TST, plus either sleep efficiency ≤85% or sleep onset time >25 min at baseline PSG. Exclusion: clinically relevant sleep apnea (>20 episodes/h) or fewer episodes but with a repeated O2 saturation <80% or other specific primary sleep disorders; previous treatment with pergolide or cabergoline; and serum iron level <6.3 µmol/L, total iron binding capacity >71.6 mmol/L, or serum ferritin<16.4 mg/L in men or <6.9 mg/L in women. Any medication known to improve RLS symptoms had to be stopped before visit 2.	Not stated	100 / 56.2 / majority women	Nausea and headache were more frequent with pergolide than placebo treatment. In phase 1, treatment-emergent adverse events irrespective of causality assessment occurred in 31 (67.4%) of 46 pergolide patients and 29 (54.7%) of 53 placebo patients (p=0.2). The most common adverse events in patients receiving double-blind and open-label pergolide were nausea, headache, abdominal pain, and vomiting. 9 patients discontinued due to AE: 5 nausea 2 asthenia, 1 decreased libido, 1 somnolence.	Patient Global Impression, PGI, scale; PSG-monitored sleep efficiency (SE) and periodic limb movements during sleep (PLMS) arousal index; IRLS Phase 1: Pergolide reduced PLMS arousal index vs placebo -12.6 ± 10.0 vs -3.6±15.9; p=0.004 SE did not improve 11.3±11.9% vs 6.1±18.6%, p=0.196 IRLS improved -12.2±9.9 vs-1.8±7.5, p<0.001 Higher PGI response 68.1% vs 15.5%, p<0.001 Improvements in PLM index, PGI improvement scale, CGI improvement, IRLS (all p<0.001), patient-reported SE (p=0.019), and quality of sleep (p<0.001). After 12 months, improvements in PLMS arousal index and PLM index maintained.	Pergolide substantially improves periodic limb movement measures and subjective sleep disturbance associated with RLS. Low-dose pergolide was well tolerated and maintained its efficacy in the long term.	
Trenkwalder, 2004 (50) **TREAT RLS 1 Study**	Men and women aged 18 to 79 years. All participants had a score of >15 on the international restless legs scale (IRLS) and had either experienced at least 15 nights with symptoms of RLS in the previous month or, if receiving treatment, reported they had had symptoms of this frequency before treatment. Patients were excluded if they were suffering from other movement or primary sleep disorders, if they required treatment for RLS during the daytime (defined as 10.00 to 18.00 hours), if they were experiencing augmentation or end of dose rebound, or if they had RLS associated with end stage renal disease, iron deficiency anaemia, or pregnancy. Patients were also excluded if they had a history of alcohol or drug abuse, had previous intolerance to dopamine agonists, or were suffering from other clinically relevant conditions affecting assessments.	≥15 on IRLS (at least mid-moderate)	284 (112/146 ropinirole and 109/138 placebo completed) / 54.0 (11.1) 30-78 Ropinirole; 56.2 (11.2) 28-77 placebo / 88F58M Ropinirole; 91F47M placebo	The most common adverse events were nausea and headache. Most events were mild to moderate in intensity . The frequency of adverse events declined over time in both groups: after day 70, only 9.6% (14 patients) in the ropinirole group and 5.8% (eight patients) in the placebo group reported new adverse events. There were no reports of augmentation.	Total RLS score; Global improvements (clinical global impression (CGI) scale) and improvements in sleep, health related quality of life (QoL; using generic and disease specific measures), work, and other activities were also assessed. Improvement in IRLS at week 12 with ropinirole was greater than with placebo (mean (SE): -11.04 (0.719) v -8.03 (0.738) points; adjusted difference =23.01 (95% confidence interval (CI), -5.03 to -0.99); p = 0.0036). More patients in the ropinirole group (53.4%) showed improvement on the CGI scale at week 12 than in the placebo group (40.9%; adjusted odds ratio = 1.7 (1.02 to 2.69); p = 0.0416). Significant differences on both IRLS and CGI scales favouring ropinirole were apparent by week 1. Ropinirole was also associated with significantly greater improvements in sleep and QoL end points.	Ropinirole improves restless legs syndrome compared with placebo, with benefits apparent by week 1. It is generally well tolerated.	
Trenkwalder, 2006 (44)	For Period 1, patients 18 to 80 years of age were recruited from 13 sites in Germany with symptoms at least 2 to 3 days per week for the previous 3 months, and at baseline (the start of Period 1) had an IRLS score > 15. (Among patients who later entered Period 2, the mean was 28.4.) To enter Period 2, they were required to have responded to pramipexole (CGI-I rating of "very much improved" or "much improved" and an IRLSSG Rating Scale total score ≤ 15), with ≥ 80% compliance and no dose adjustments during the final 12 weeks of Period 1. Patients were excluded for use of L-dopa (the preceding week) or other drugs known to influence RLS (the preceding 2 weeks); for medical conditions that might affect assessment of RLS; for any specific sleep disorder; for failure of prior pramipexole treatment; and (among fertile females) for pregnancy or inadequate contraception.	Not stated	150	The great majority of adverse events (AEs) were mild or moderate, and of expected types. Augmentation was considered an AE, but in this population of responders it did not occur. Five types of AEs had overall frequencies 2%: worsening RLS (5.5% for placebo vs. 6.4% for pramipexole), nasopharyngitis (1.4% vs. 3.8%), diarrhea (1.4% vs. 3.8%), vomiting (2.8% vs. 2.6%), and upper abdominal pain (0% vs. 3.8%). Only 5 patients (3.3%) had AEs classified as severe: 3 in the placebo group (all worsening of RLS) and 2 in the pramipexole group (1 forearm fracture and 1 worsening of RLS).	For Period 2, the primary outcome was the time to insufficient response, as defined by concurrence of two independently rated parameters: a CGI-I score of "minimally," "much," or "very much" worse (compared with the score at the start of Period 2), and an increase of the IRLS to a score > 15. Secondary outcome measures were the CGI-I rating; other CGI subscales; the Patient Global Impression scale (PGI); the Johns Hopkins Restless Legs Syndrome Quality of Life questionnaire (RLS-QOL); the 10-cm visual analogue scales (VAS) for RLS severity while getting to sleep, during the night, and during the day, and for satisfaction with sleep the previous week (modified RLS-6 scale); and the ESS of daytime somnolence. Patients switched to placebo reached the primary endpoint significantly more often than patients who continued to receive pramipexole (85.5% vs.20.5%; P < 0.0001). They also reached the primary endpoint faster, in 5 versus 42 days to a Kaplan–Meier survival estimate of 0.85 and 7 versus 84 days to an estimate of 0.5. Over the total 9 months, clinician and patient ratings of symptoms, sleep, and quality of life identified no decline in pramipexole's benefit or tolerability.	The 9-month results show no decline in either the efficacy or safety of pramipexole for RLS. It may be concluded, therefore, that patients who respond well to pramipexole within the first weeks are good candidates for a long-term response.	
Trenkwalder, 2007 (67) CALDIR Trial	Patients with moderate to severe idiopathic RLS. Male and female patients aged 18 to 75 years could participate in the study if they presented with all four clinical manifestations of RLS according to the IRLSSG criteria. Patients were either de novo or unsatisfied with previous RLS therapy. Patients with secondary RLS, iron deficiency, or other clinically relevant concomitant diseases were excluded. Patients with established or suspected hypersensitivity to ergot alkaloids or with non-response or intolerability to previous cabergoline or L-dopa therapy, if any, were also excluded.	Severity of symptoms had to be at least moderate according to the IRLS total score (IRLS score 10 or higher). In addition a "severity at night" score of ≥ 4 in the 11-point RLS-6 rating scale (ranging from 0 = "not present" to 10 = "very severe") had to be present. Title of paper says "severe"	361 of 418 screened patients (age 58 ± 12 years, 71% females) (204 completed)	Adverse events (AEs) occurred in 83.1% of the CAB group and in 77.6% of the levodopa group. In both groups, most frequent AEs were gastrointestinal symptoms (CAB: 55.6%, levodopa: 30.6%, P < 0.0001). According to the CGI "side effects" (investigator assessment) were better tolerated with L-dopa than with cabergoline (no or mild side effects: 95.5% in the L-dopa group, 85% in the cabergoline group, P 0.0056), no difference was found in the patients' assessments.	Efficacy was assessed by changes in the IRLS (International RLS Severity Scale) and by time to discontinuation of treatment due to loss of efficacy or augmentation. Baseline IRLS total score was 25.7 ± 6.8. The baseline-adjusted mean change from baseline to week 6 in IRLS sum score was d = -16.1 in the CAB group and d = - 9.5 in the levodopa group (d = - 6.6, P < 0.0001). More patients in the levodopa group (24.0%) than in the CAB group (11.9%, P = 0.0029, log-rank test) discontinued because of loss of efficacy (14.2% vs. 7.9%, P = 0.0290) or augmentation (9.8% vs. 4.0%, P = 0.0412).	This first large-scale active controlled study in RLS showed superior efficacy of cabergoline versus levodopa after a 30-week long-term therapy. Tolerability was found more favorable with levodopa than with cabergoline.	
Trenkwalder, 2008 (109) **ClinicalTrials.gov number NCT00136045**	Moderate-to-severe idiopathic RLS. Inclusions: Age 18–75 years; de novo or previous positive response to dopaminergic treatment;IRLS scale ≥ 15; ≥ 4 for the CGI item 1 assessment, the ability to remove and apply patches correctly and consistently. Exclusions: secondary RLS; current history of sleep disturbances (sleep apnea syndrome, narcolepsy, myoclonus epilepsy, daytime sleep attacks); concomitant treatment with several types of drugs; concomitant diseases (polyneuropathy, akathisia, claudication, varicosis, muscle fasciculation, painful legs and moving toes, or radiculopathy); other CNS diseases; previous psychotic episodes; skin hypersensitivity to adhesives or other transdermal preparations; recent myocardial infarction; clinically relevant cardiac, renal, or hepatic dysfunction; arterial peripheral vascular disease; a QTc interval ≥500 ms; symptomatic orthostatic hypotension; intake of an investigational drug in the previous 28 days; pregnant,lactating, or non-effective contraceptive women; work-related irregular sleep patterns.	Moderate to severe	458 (313) / Rotigotine 1 mg: 57·3 (10·1) Rotigotine 2 mg: 57·3 (12·1) Rotigotine 3 mg: 56·5 (12·0) Placebo: 59·7 (10·0) / Rotigotine 1mg: 34 (28%) M, 81 (72%)F; Rotigotine 2 mg: 27 (25%)M, 82 (75%) F; Rotigotine 3 mg: 30 (27%) M, 82 (73%) F; Placebo: 34 (30%) M , 80 (70%) F	Skin reactions, mostly mild or moderate, were seen in 145 (43%) of 341 patients who received rotigotine and in two (2%) of 117 who received placebo. Ten patients had serious adverse event that were deemed to be related to rotigotine: elevation of liver enzymes (one patient), worsening of tinnitus (one patient), non-response to anticoagulation (one patient), electrocardiogram changes (one patient), and application-site reactions (six patients). No admissions to hospital were needed for the application-site reactions, and they all resolved within a short time of patch removal without any other therapeutic intervention. The rate of typical dopaminergic side-eff ects in patients who received rotigotine was low; no signs of augmentation were noted.	Primary efficacy outcomes were absolute change from baseline to end of maintenance in IRLS sum score and in the clinical global impressions (CGI) item 1 score, assessed by analysis of covariance in the intention-to-treat population. Mean change in IRLS sum score from baseline at the end of the maintenance phase was −13·7 (SE 0·9) in the 1 mg group, −16·2 (0·9) in the 2 mg group, −16·8 (0·9) in the 3 mg group, and −8·6 (0·9) in the placebo group (p<0·0001 for treatment difference vs placebo with each dose). Mean change in CGI item 1 score from baseline at the end of the maintenance phase was −2·09 (0·14) in the 1 mg group, −2·41 (0·14) in the 2 mg group, −2·55 (0·14) in the 3 mg group, and −1·34 (0·14) in the placebo group (p<0·0001 for treatment difference vs placebo with each dose).	24 h transdermal delivery of low-dose rotigotine could be used to relieve the night-time and daytime symptoms of restless legs syndrome.	
Walters, 2001 (79)	Patients on opioid therapy either alone (36 patients) or secondary to other medications used to treat RLS (77 patients)	Not described	113 / 37–88 years / 51M 62F	Addiction and tolerance were extremely uncommon, encountered in only 1 of the 36 patients on monotherapy.The eight patients who discontinued monotherapy because of side effects did so because of increase in daytime fatigue (three patients), and one patient each had migraine headache, hangover and grogginess, paradoxical hyperalerting response, constipation, and nonspecific side effects.	Twenty of the 36 opioid monotherapy patients continue on monotherapy for an average of 5 years 11 months (range, 1–23 years), despite their knowledge of the availability of other therapies. Of the 16 patients who discontinued opioids as a sole therapy, the medication was discontinued in only one case because of problems related to addiction and tolerance. Polysomnography on seven patients performed after an average of 7 years 1 month of opioid monotherapy (range, 1–15 years) showed a tendency toward an improvement in all leg parameters and associated arousals (decrease in PLMS index, PLMS arousal index, and PLM while awake index) as well as all sleep parameters (increase in stages 3 and 4 and REM sleep, total sleep time, sleep efficiency, and decrease in sleep latency). Two of these seven patients developed sleep apnea and a third patient had worsening of preexisting apnea.	Opioids seem to have long-term effectiveness in the treatment of RLS and PLMS, but patients on long-term opioid therapy should be clinically or polysomnographically monitored periodically for the development of sleep apnea. Twenty of 36 patients who had ever tried opioids as a monotherapy continue this therapy after an average of 5 years 11 months, with a range of 1–23 years. This was despite their knowledge of the availability of other therapies. In our opinion this strongly attests to the efficacy of the opioids in RLS.	23/36 opioid monotherapy patients had failed dopaminergic and other therapeutic agents prior to the initiation of opioid monotherapy. The optimal opioid has not been determined, but our clinical experience suggests matching the strength of the opioid to the severity of the patient's symptoms. Propoxyphene, a relatively weak opioid, that may help mildly affected patients is not useful for severe cases. For cases of intermediate severity we find that oxycodone and codeine, available in the US, and tilidine and dihydrocodeine, available in Europe, are therapeutically successful. We reserve methadone, an opioid with a long half-life, for our most severely affected patients and in such cases it may be very effective.
Walters, 2004 (51) **TREAT RLS 2 Study**	Inclusions: Males or females 18 - 79 years of age, attending 46 centers in Australia, Europe, and North America, with primary, moderate-to-severe RLS; A score at baseline of ≥15 on the IRLS Severity criteria; ≥ 15 nights of RLS symptoms during the previous month; patients with daytime RLS symptoms unless they suffered from symptoms that required treatment during the day. Exclusions: Patients suffering from augmentation or end-of-dose rebound with previous medication; known causes of secondary RLS (renal failure, iron-deficiency, pregnancy, or clinical peripheral neuropathy), other sleep disorders (e.g., narcolepsy, sleep terror disorder, sleepwalking disorder, breathingrelated sleep disorder), other movement disorders, or from any medical conditions that would affect the assessment of RLS (e.g., rheumatoid arthritis, fibromyalgia syndrome); patients taking any other medications known to affect sleep or RLS, those with a known intolerance to ropinirole, or those abusing substances.	≥15 on IRLS (at least mid-moderate)	267 (102/131 Ropinirole and 107/136 placebo completed) / Ropinirole: 54.9 (10.87)Range [29-77]; Placebo: 56.0 (11.25) Range [29-79] / Ropinirole 76F55M; Placebo 83F/52M	Adverse events were typical for dopamine agonists; disease augmentation, although not directly assessed, was not reported during treatment. A total of 112 patients in the ropinirole group (112/131, 85.5%) and 102 patients in the placebo group (102/136, 75.0%) reported at least one adverse event during treatment. The most common adverse events, reported by at least 10% of patients in either group, are nausea, headache, fatigue, dizziness, upper respiratory tract infection, and vomiting. All of these events, except headache, occurred in a higher proportion of patients receiving ropinirole than those taking placebo. Most of the adverse events were mild or moderate in severity.	The primary endpoint was the change in IRLS score at week 12. Key secondary endpoints were the percentage of patients showing significant improvement on the Clinical Global Impression-Improvement (CGI-I) scale at week 12 and changes in IRLS and CGI-I scale scores at week 1. Other measures included the Medical Outcomes Study sleep scale and Restless Legs Syndrome Quality of Life questionnaire. Improvements were significantly greater for ropinirole than placebo for change in IRLS score at week 12 (-11.2 [SE 0.76] vs. -8.7 [0.75], respectively; adjusted treatment difference - 2.5 [95% confidence interval [CI], - 4.6, - 0.4], P= 0.0197); all key secondary endpoints; sleep and QoL parameters.	Ropinirole improves symptoms, associated sleep disturbance, and QoL of RLS patients and is generally well tolerated.	

Evidence Table
The Treatment of RLS and PLMD in Adults

Reference (Last name, year) (Reference #)	Inclusion/ Exclusion criteria	RLS Severity	Sample size (completed) / mean age (age range or standard deviation) / gender of subjects	Adverse effects	Outcome measures / results	Conclusions	Comments
Walters, 2009 (84)	Treatment-naive subjects aged 18 to 69 years with a diagnosis of moderate-to-severe primary RLS (International RLS Study Group diagnostic criteria)1 were included. Eligible subjects were required to have RLS symptoms for 15 nights or longer during the month before screening, documented RLS symptoms for 4 nights or longer during the 7-day baseline period, and an International Restless Legs Scale (IRLS) total score of 15 or higher at the beginning and end of the baseline period. Any subject experiencing RLS symptoms during the daytime (between 10:00 AM and 6:00 PM) for 2 days or longer during the week before baseline was excluded. Subjects were also excluded if they were pregnant or lactating, had a body mass index of more than 34 kg/m2, a serum ferritin level of lower than 20 Kg/mL, an estimated creatinine clearance of less than 60 mL/min, or were currently experiencing or being treated for moderate-to-severe depression, or a neurologic, movement, or primary sleep disorder other than RLS. Use of, or any prior exposure to, dopamine agonists, gabapentin, and L-dopa/carbidopa before or during the study was prohibited.	Moderate to severe	95 (93) / 50.5 (11.17) / 38% Male	Two subjects (GEn at 1200 mg) withdrew prematurely because of AEs. One developed feelings of being drunk and withdrew before the day 7 efficacy assessment and was included only in the safety population. The second discontinued because of sedation after the day 7 assessment and was included in both safety and ITT populations.	The mean (SD) change from baseline IRLS total score at day 14 (end of treatment) was significantly greater with GEn at 1200 mg (-16.1 [7.93]) compared with placebo (-8.9 [7.72]; least-squares [LS] mean treatment difference,-7.2; P < 0.0001). The mean (SD) day 7 change from baseline IRLS total score was -14.2 (8.49) with 1200 mg and -7.8 (6.36) with placebo. Investigator-rated Clinical Global Impression-Improvement scale responses also significantly favored GEn at 1200 mg compared with placebo (P < 0.0001). The mean (SD) change from baseline IRLS total score with GEn at 600 mg at day 14 was -9.1 (5.95), similar to placebo. The most commonly reported treatment-emergent adverse events were somnolence (GEn: 1200 mg, 36% and 600 mg, 14%; placebo, 15%) and dizziness (GEn: 1200 mg, 18% and 600 mg, 14%; placebo, 3%), most of which were rated mild or moderate in intensity.	Gabapentin enacarbil at 1200 mg significantly improved restless legs syndrome symptoms compared with placebo. Efficacy outcomes for GEn at 600 mg were similar to placebo. Both GEn doses were generally well tolerated.	
Wang, 2009 (100)	Patients gave written consent to be contacted if they met NIH diagnostic criteria for RLS and received a score of ≥11 using the validated IRLS. Only those patients with a measured ferritin level of 15–75 ng/ml were included in the study. Patients were excluded from the study for pregnancy, hemochromatosis or other significant liver disease, end-stage renal disease, significant sleep disturbances for reasons other than RLS (i.e., known obstructive sleep apnea, periodic limb movements of sleep, etc.), iron saturation less than 15%, hemoglobin levels less than 11.1 g/dL for females and 14 g/dL for males, iron sulfate allergy, current or recent treatment with iron sulfate as defined by more than 325 mg each day for at least half of the days in the past 2 months or any other potential medications for treatment of RLS.	≥11 on IRLS	18 (18)/33-82 (mean iron: 60, mean placebo: 58)/ 7M 11F	Not stated	The mean baseline IRLS scores for iron and placebo groups were 24.8 ± 5.72 and 23.0 ± 5.03, respectively (p = 0.49). Mean decreases in IRLS score after 12 weeks for iron and placebo groups were 10.3 ± 7.40 and 1.14 ± 5.64, respectively (p = 0.01). The mean baseline serum ferritin levels for the iron group were 40.6 ± 15.3 ng/ml and 36.7 ± 20.8 ng/ml for the placebo group (p = 0.68). The mean change in serum ferritin after 12 weeks for the iron group was 25.1 ± 20.3 ng/ml and 7.5 ± 13.7 ng/ml for the placebo group (p = 0.04). When comparing dichotomized variables at baseline and at week 12, a nonsignificant trend toward improved quality of life was seen between iron and placebo groups (p = 0.07)	This is the first double-blinded, placebo-controlled study to demonstrate statistically significant improvement in RLS symptoms using oral iron therapy in patients with low-normal ferritin	The findings from this study suggest that additional larger randomized placebo-controlled trials of iron as treatment for patients with low-normal ferritin are warranted.
Winkelman, 2004 (46)	Patients who were maintained on pramipexole for at least 6 months with regular clinical contact were eligible for entry into this retrospective naturalistic study. Those who had been on pramipexole less than 6 months at the time of this chart review (N = 5); or who discontinued pramipexole before 6 months of treatment due to side-effects or ineffectiveness (N = 6); or did not maintain regular contact (N = 2); were excluded from further analysis. Thirteen of the patients (22%) had secondary RLS (8 neuropathy, 2 end-stage renal disease, 1 Parkinson's, 1 anemia, 1 multiple sclerosis).	Not stated	59 / Mean age was 60.8 years (±14.4; range 31–91); 34 were female (58%), 25 were male (42%)	The mean time to the first episode of augmentation was 8.8 months (±6.5). For two patients this occurred after 1–3 months on pramipexole, for six it occurred after 4–6 months, for eight it occurred after 7–12 months, and for two it occurred after greater than 12 months. Only one patient discontinued pramipexole due to the development of augmentation.	Augmentation developed in 32% (19/59), and tolerance occurred in 46% (27/59), of patients. These two complications were statistically related (P < 0:05). The only clinical predictors of these complications were previous augmentation or tolerance to L-Dopa. New onset of morning symptoms ('rebound') was not reported by those on long-term pramipexole treatment.	Augmentation and tolerance are more common with extended pramipexole treatment of RLS than has been previously reported in preliminary studies. However, these complications are generally manageable by earlier dosing or small dose increases of this agent, and only rarely require medication discontinuation.	
Winkelman, 2006 (31) **PIRLS Study**	Patients with moderate to severe restless legs syndrome (RLS). Men and women aged 18 to 80 years were recruited at 43 sites in the United States. To be eligible, patients were required to have had symptoms at least 2 to 3 days per week for at least the previous 3 months and to have a baseline score < 15 on the IRLSSG Rating Scale, representing moderate to severe symptomatology. Patients were excluded for recent RLS treatment (concurrently or during the prior 2 weeks), for a history of failed RLS treatment, for recent use of any dietary supplement or medication with potential to affect RLS symptoms, for any medical condition that could affect assessment or contraindicate pramipexole, and for any sleep disorder other than RLS. Additionally, women of childbearing potential were excluded for inadequate contraception or a positive baseline serum pregnancy test.	Moderate to severe; IRLS>15 at baseline	344 (281) / 51.4 (SD=13.0) / 62.2%F	Pramipexole was well tolerated: The most frequent adverse events with higher occurrence in the pramipexole group were nausea (19.0% vs 4.7%) and somnolence (10.1% vs 4.7%)	The primary efficacy endpoints were patient ratings of symptom severity on the IRLSSG Rating Scale and clinician ratings of improvement on the CGI-I scale. Secondary efficacy endpoints included visual analogue ratings of sleep and quality of life (QOL). By both primary measures, pramipexole was superior to placebo. For IRLS, the adjusted mean (SE) change from baseline to week 12 was - 9.3 (1.0) for placebo, -12.8 (1.0) for 0.25 mg/day, -13.8 (1.0) for 0.50 mg/day, and -14.0 (1.0) for 0.75 mg/day (all p< 0.01). Similarly, pramipexole increased the percentage of patients with a CGI-I rating of "very much improved" or "much improved" at the end of the trial (51.2% for placebo and 74.7%, 67.9%, and 72.9% for pramipexole; all p < 0.05). Pramipexole significantly improved ratings of symptom severity, day and night, and also ratings of sleep satisfaction and QOL. Pramipexole was well tolerated.	As rated by patients and by clinicians, pramipexole was efficacious and safe in reducing the symptoms of restless legs syndrome initiall rated as moderate to severe.	A noteworthy finding is that the therapeutic effects of pramipexole, as measured by PGI, were apparent within 1 week of initiating treatment, and therefore at 0.125 mg/day. Another noteworthy finding is that the effects of pramipexole generally were not dose-related among the fixed doses of 0.25, 0.50, and 0.75 mg. On both of the primary endpoints, a substantial placebo response was observed.
Zucconi, 2003 (65)	patients with moderate to severe RLS who were naive to treatment with dopaminergic agents. All patients had been previously treated with benzodiazepines (1 with benzodiazepines and opioids) but none had ever used DAs, and all refrained from using any drugs for at least 3 weeks before the study began.	Moderate to severe	12 (10) / mean age 56.6 years (range, 38-73) / 4F8M	Two patients dropped out after the first week of treatment with cabergoline (T1) due to marked nausea (N=1) and ineffectiveness (N=1).	Patients were evaluated with polysomnography at baseline (B), following 1 week of placebo (T0), and after 1 week (T1) and 2 months (T2) of cabergoline treatment. The clinical global impression was assessed using International RLS Study Group Rating Scale and nocturnal actigraphy. All showed an improvement of RLS symptoms. The results from the International RLS Study Group Rating Scale showed similarities between B (24.3±2.9) and T0 (23.1±5.9; P=0.6), with significant improvement at T1 (12.5±6.0; P=0.01 vs B and T0) and T2 (9.8±6.9; P=0.001 vs B and P=0.005 vs T0). The mean nocturnal activity value measured by actigraphy during week 1 decreased from T0 (19.8±9.3) to T1 (13.6±6.4) and dropped significantly at T2 (8.5±5.3; P=0.05). Nine patients continued the treatment up to 12 months with consistent efficacy, few side effects, and no augmentation	Low doses of cabergoline showed effectiveness and safety in patients with moderate to severe RLS, with no appearance of augmentation phenomenon. In conclusion, our study confirms the efficacy of cabergoline, a dopaminergic agent with a long half-life, as single drug for patients with moderate to severe RLS and for short-term to intermediate-term treatment. Moreover, as opposed to L-dopa and other DAs, cabergoline seems to be relatively safe and causes less augmentation, suggesting a relevant role in RLS treatment.	Suggest conducting a double-blind, randomized, long-term, crossover study using PSG with a larger sample of patients to confirm preliminary data