D.3.2 Nocturnal akinesia

Bibliographic reference	Trenkwalder,C., Kies,B., Rudzinska,M., Fine,J., Nikl,J., Honczarenko,K., Dioszeghy,P., Hill,D., Anderson,T., Myllyla,V., Kassubek,J., Steiger,M., Zucconi,M., Tolosa,E., Poewe,W., Surmann,E., Whitesides,J., Boroojerdi,B., Chaudhuri,K.R., Rotigotine effects on early morning motor function and sleep in Parkinson's disease: A double-blind, randomized, placebo-controlled study (RECOVER), Movement Disorders.26 (1) (pp 90-99), 2011.Date of Publication: January 2011., 90-99, 2011
Country/ies where the study was carried out	Germany
Study type	Double-blind placebo controlled randomized controlled trial
Aim of the study	To reduce motor disability and improve sleep in patients with Parkinson's disease
Study dates	Paper received 22 June, accepted August 2010, published Nov 2010
Source of funding	RECOVER study supported by Schwartz Biosciences GmbH, a member of UCB group
Sample size	N=287; rotigotine n=2190, placebo n = 97
Inclusion criteria	Subjects with diagnosis of PD and unsatisfactory early-morning motor symptom control. Patients were age >18 years, PD H&Y stage1-4 (both fluctuators and non-fluctuators), and unsatisfactory control of early morning motor symptoms as determined by the investigator . PD defined by presence of bradykinesia and at least 1 of the following: resting tremor, rigidity, impairment of postural reflexes subjects taking immediate release L-dopa or not taking L-dopa were included as long as had been on stable dose for <28 days prior to baseline
Exclusion criteria	None
Details	Antiemetics without central dopaminergic activity were permitted. ACTHI#s MOABI's, NMDA's, entacapone, sedatives, hypnotics, SSRIs, anxiolytics, and other CNS medications were permitted providing dose was stable for >28 days prior to baseline. Controlled-release L-dopa, other centrally acting dopaminergic agents MOA-B inhibitors, tolcapone, budipine, neuroleptics (except olanzapine, ziprasidone, ariprazole, clozapine, or quetiapine) were prohibited from 28 days prior to baseline screening took place 4 weeks before baseline. subjects randomizes 2:1 to receive rotigotine or placebo, stratified by site, using computerized randomization schedule. clinic visits took place at screening, and baseline. Every 2 weeks. during dose titration, start and end of maintenance, 30 days post treatment ending. Efficacy assessments performed after first or second night of hospitalization at baseline and at end of maintenance or withdrawal

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	safety and tolerability assessed throughout study and up to 30 days after treatment discontinuation by monitoring frequency and severity of AE's and any changes in vital signs. Emergence of ICD monitored using modified Minnesota impulsive disorder interview (mMIDI)
Interventions	Rotigotine transdermal patch; Day 1, treatment administered once daily in morning using 24hr transdermal patch with identical-looking placebo patch Treatment titrated to optimal dose over 1-8 weeks. starting at 2mg/24hr and increasing in weekly increments of 2mg/24hr up to a maximum of 16mg/24hr Dose maintained at optimal or maximal dose for 4 weeks during which dose reduction not permitted During titration, dose could be back-titrated once if adverse events occurred that were thought to be because of excessive dopaminergic action. Subjects requiring back-titration immediately entered into maintenance period
Results	Baseline characteristics were similar between treatment groups. 80/97 completed placebo: 7 withdrew consent, 6 adverse events, 4 lack of efficacy; 89 included in efficacy analysis, 96 included in safety analysis 166/190 completed rotigotine: 11 withdrew consent, 11 adverse events, 2 other reasons. 178 included in efficacy, 191 in safety NB* q subject in placebo group received 1 dose of rotigotine during de-escalation to counted in this group for safety. Efficacy outcome: Improvement in UPDRS III-motor score MD = -3.55 (-5.37to -1.73) Improvement PDSS-2 total score MD = -4.26 (-6.08 to -2.45) Improvement in NADCS total score MD = -0.41 (-0.79 to -0.04) No significant effect on number of nocturias MD = -0.02 (-0.29 to 0.25) Mean NMS improved MD = -6.65 (-11.99 to -1.31) Improvement in UPDRS II (ADL) MD = -1.49 (-2.32 to -0.65) Improvement in health related quality of life PDQ8 MD = -5.74 (-8.74 to -2.75) Safety and tolerability Mean duration drug exposure 73 days in placebo and 71 in rotigotine 80% subjects compliant overall

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	Most frequently reported AE = nausea, application and installation site reaction, dizziness, dyskinesia, headache. total 54/96 placebo, 137/191 rotigotine, - (Risk ratio calculated using RevMan: RR= 3.07, 95%CI = 0.08 to 11.3
Overall Risk of Bias	NICE RCT checklist: 1. An appropriate method of randomization was used to allocate pts to treatment groups? Yes - computer randomized sequence. 2. There was adequate concealment of allocation: Yes - double blind 3. The groups were comparable at baseline, including all major confounding and prognostic factors? Yes - comparable at baseline 4. Comparison groups received same care apart from interventions: yes 5. Pts receiving care were kept blind to tmt allocation: Yes - patients and practitioners were blind 6. Individuals administering care were kept blind to tmt allocation: Yes - blind assessors 7. All groups followed up for an equal length of time: yes - equal time follow-up 8. Groups comparable for treatment completion? Yes - similar completion in both arms 9. Groups were comparable with respect to availability of outcome data? Yes 10. Study had appropriate length of follow up Yes - 30 days follow up. Drug exposure average 78 days 11. Study used a precise definition of outcome Yes - clearly defined outcomes 12. Valid and reliable method was used to determine the outcome: yes- well-validated outcome measures 13. Investigators were kept blind to participants' exposure to the intervention: yes - blind assessors 14. Investigators were kept blind to other important confounding and prognostic factors: not clear whether assessor had access to medical notes. Overall quality = HIGH (risk of bias = low)
Other information	None

Evidence Table Q TxCM8 What is the effect of controlled-release levodopa vs. immediate-release levodopa in the treatment of later Parkinson's disease?	
Bibliographic reference	The U.K.Madopar CR Study Group. A comparison of Madopar CR and standard Madopar in the treatment of nocturnal and early-morning disability in Parkinson's disease. Clin Neuropharmacol 1989;12:498-505.
Study type	Double-blind crossover study
Evidence level	1+
Study objective	To compare the effects of Madopar CR with that of conventional Levodopa/benserazide (Madopar) on nocturnal and early morning disability in patients with Parkinson's disease.
Number of patients	N=103 patients with Parkinson's disease (PD) Location: UK Sites: 11 centres
Patient characteristics	Majority of patients had difficulty turning in bed or getting out of bed and suffered from cramps and pain at night; foot spasms and spontaneous jerks were also common. The mean age was 67.7 years and 67% of the population was male. Disease duration ranged from 1 to 29 years, with a mean of 8 years. Mean duration of levodopa therapy was 6.4 years. The majority of patients (52%) were rated as Hoehn and Yahr stage III, 26% were stage II, 19% were stage IV and 2% were stage I. Daytime fluctuations in response to levodopa and/or abnormal involuntary movements were reported by 42 of 103 patients (41%).
Intervention	Controlled-release Madopar 125 mg (CR) immediately before going to bed. If insufficient effect on symptoms was observed, the dose was increased by 125mg weekly to a maximum of 4 capsules at night. Once optimum night time dose was determined, patients remained at this dosage for 2 weeks. They then transferred to alternative treatment, starting at one capsule, the procedure was repeated.
Comparison	Standard Madopar 125 mg immediate-release (IR) immediately before going to bed
Length of follow-up	Trial duration: 6 weeks (3 weeks per arm). No follow-up stated
Outcome measures	Patient diaries and opinion of investigator
Effect size	82/103 patients completed the study Dosage Mean optimum dosages for the treatments was similar (2.4 capsules for CR, 2.2 for IR) Sleep On entry to study mean time taken to fall asleep (recoded by investigator) was 47 min During optimum treatment periods this time was reduced to 38 min (CR) and 39 min (IR) Mean time taken to fall asleep (patient diaries) was little different between treatments

	Both CR and IR reduced total nocturnal and early-morning disability scores recorded by investigator compared with baseline to a statistically significant degree Little difference between total scores for two optimum treatment periods for either nocturnal or early-morning disability Nocturnal and early-morning disability scores taken from patient diaries and averaged over the periods of optimum treatment were also very similar for IR and CR Patient ratings of early morning condition also improved from baseline but not between treatments The majority of patients considered their overall nocturnal condition was better after optimum treatment with either IR or CR than on entry to study 62% of patients felt better after CR and 59% felt better after IR The number of patients who felt their nocturnal condition was worse from baseline was 4% CR and 10% IR Overall early-morning condition was rated as better than on entry to the study was 46% after CR and 45 after IR Percentage of patients who felt overall condition was worse was 2% cr and 6% IR 2/3 of patients gave the same response for both treatments with respect to their effect on overall condition compared to baseline Only 27% felt the two treatments were the same in relation to their effect on nocturnal condition 41% felt CR was better 33% felt it was worse Corresponding percentages for early-morning condition are 41% the same, 33% felt CR was better and 26% felt CR was worse CR was considered to be advantageous by 61% of patients and IR by 60% Patients who found treatments to be disadvantageous: 23% CR and 28% IR After the optimum treatment period the investigator (patient) felt it was justified to continue treatment with CR 55% (63%) of cases and with IR in 50% (55%) of cases Good agreement between patient and investigatory opinions Despite many little differences between treatments investigator thought that there was a difference between the two treatments in 60% of cases Of these CR was felt to be preferable in 65% and IR in 35% Adverse effects 63 adverse events were reported by 37 patients (32 CR and 31 IR)

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	Majority were consistent with levodopa profile Dyskinesia was the most commonly reported adverse event (8 CR, 7 IR) Other adverse events: disorders of movement, gastrointestinal, central effects such as confusion, expression, hallucinations etc was evenly distributed between the 2 treatments Withdrawal rates 21 patients withdrew Lack of effect was the reason given in 3 cases (one on IR and 2 on CR) Adverse side effects in 11 cases (4 on IR and 7 on CR) 7 due to other reasons
Source of Funding	Not stated
Additional comments	There was no washout period between arms and no first arm results were reported Period and carry-over effects were analysed Differences from baseline to the end of the first treatment period were assessed within each treatment group separately, also using analysis of variance techniques Methods of randomisation or allocation concealment not stated No sample size calculations Intention-to-treat not stated Centre comparisons were performed No details of blinding procedure No details of clinical diagnosis criteria