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Original Article

# Effectiveness and tolerability of rotigotine transdermal patch for the treatment of restless legs syndrome in a routine clinical practice setting in Germany

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ABSTRACT

*Objective:* We aimed to assess effectiveness and tolerability of rotigotine in patients with moderate to severe idiopathic restless legs syndrome (RLS) under daily practice conditions in Germany.
*Methods:* In this 3-month noninterventional study, effectiveness was assessed using RLS-6 (primary variables were symptom severity when falling asleep [item 2] and during the night [item 3]). Data were collected at baseline and at the end of treatment. Safety assessments included adverse events (AEs).
*Results:* Six hundred and eighty-four patients were treated with rotigotine and 418 (61%) completed the study. The full analysis set (FAS) comprised 564 patients (106 de novo; 458 pretreated [454 had complete rotigotine dosing data]). Mean rotigotine dose of longest duration was 2.4 ± 1.4 mg/24 h. Rotigotine improved all RLS-6 items (mean change from baseline [item 2], −2.4 ± 3.6; [item 3], −2.7 ± 3.4), with the most pronounced improvement observed in daytime symptoms while at rest (item 4, −2.9 ± 3.2). AEs were typical of dopaminergic treatment and transdermal administration. De novo patients generally started rotigotine on 1 mg/24 h (85% [90/106]) and pretreated patients on 1 (50% [227/454]) or 2 mg/24 h (40% [183/454]). Most patients who were pretreated with levodopa (57%), pramipexole (84%), or ropinirole (78%) monotherapy discontinued these medications on initiation of rotigotine.
*Conclusions:* Rotigotine was effective and well-tolerated when used in routine clinical practice.


## 1. Introduction

Restless legs syndrome (RLS) is a chronic sensorimotor disorder characterized by uncomfortable or unpleasant sensations in the limbs that arise during periods of rest and can be relieved by movement [1]. The disease has a circadian pattern, with symptoms predominantly occurring during the evening and at night and can result in considerable sleep disturbance [2]. Patients also experience daytime symptoms particularly as the severity of the disease progresses [3]. Dopamine receptor agonists are recommended as first-line treatment for patients with moderate to severe idiopathic RLS [4–6]. Most oral therapies for RLS are administered in the evening shortly before symptoms are expected to occur or become more severe. Rotigotine is a nonergolinic D3/D2/D1 receptor agonist [7] formulated as a transdermal patch. Continuous transdermal delivery of rotigotine maintains stable plasma levels over a 24-hour period with a single daily application [8]. The continuous dopaminergic stimulation provided by rotigotine may be particularly beneficial for patients who experience early morning and daytime symptoms in addition to symptoms during the night as well as for patients who experience fluctuations in the normal time of onset of their symptoms.

The efficacy and tolerability of rotigotine transdermal patch in adult patients with moderate to severe idiopathic RLS has been demonstrated in several placebo-controlled trials. A 6-week dose-finding trial established a therapeutic window for rotigotine in the 1- 3 mg/24 h dose range based on international restless legs syndrome rating scale (IRLS), clinical global impression (CGI), and RLS-6 scores [9]. Efficacy of rotigotine over a 6-month period was assessed in two randomized, placebo-controlled, fixed-dose trials, which used the IRLS and CGI-1 as coprimary end points [10,11]. In the European study, significant improvements were observed with 1- 3 mg/24 h doses of rotigotine vs placebo ($p < .0001$) [10], whereas the US study demonstrated superiority over placebo for

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the 2 and 3 mg/24 h rotigotine doses ($p < .001$) [11]. A 1-month sleep laboratory trial demonstrated improvements in periodic limb movement index with rotigotine [12]. Finally, the results of an open-label extension study indicated that rotigotine generally was well-tolerated and provided sustained efficacy for up to 5 years based on IRLS, CGI, and RLS-6 scores [13].

When performing clinical trials it often is necessary to exclude patients based on certain clinical characteristics such as comorbid diseases and concomitant medications and to place restrictions on the dosing of trial treatments. Although this exclusion allows a drug's effect to be distinguished from other influences enabling valid conclusions to be drawn, the clinical applicability of the results may be limited due to the clinical trial sample not fully representing patients in a real-world setting. Therefore, our study was conducted to assess the effectiveness, safety, and tolerability of rotigotine when used in general practice in Germany. Descriptive data for daytime symptoms and for switching practice from a previous RLS therapy also were collected. To our knowledge, our study is the first to investigate the effectiveness of a dopamine receptor agonist when used for RLS under daily practice conditions.

## 2. Methods

### 2.1. Design

RLS-PRACTISE (ClinicalTrials.gov: NCT01113710) was a 3-month noninterventional study conducted in a routine clinical practice setting in Germany. Patients were enrolled from a mixture of hospital-based and private clinics. Most of the sites were neurology practices, though a few sleep medicine practices also were involved. Treatment according to the European summary of product characteristics (SmPC) [14] for rotigotine transdermal patch was recommended. No further dosing recommendations were made and no criteria for the choice of starting dose were specified. Data were collected at baseline (initial visit) and end of treatment (after ~12 weeks) and data collected during the course of the study also could be documented. Additional visits were conducted at the investigator's discretion, with an optional interim visit recommended after 3 weeks of treatment, at which point the maximal rotigotine dose may have been reached according to the SmPC titration scheme. Patients were assessed per clinical practices for RLS at the time of the study and no additional diagnostic and monitoring procedures were applied.

### 2.2. Patients

Adult patients with a diagnosis of RLS who were considered to be reliable and capable of adhering to the visit schedule and medication administration were included. Rotigotine is indicated for the treatment of moderate to severe idiopathic RLS. The decision to prescribe rotigotine was made independently by the physician according to regular practice, based on their clinical judgment of what was in the best interest of the patient and was independent of the decision to include the patient in the study. Patients were excluded if they had known hypersensitivity to any components of rotigotine transdermal patch or any medical or psychiatric condition which, in the opinion of the investigator, could jeopardize or compromise the patient's ability to participate. The study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed data consent prior to participation. The study protocol, amendments, and patient informed consent were reviewed and approved by the ethics committee of the Philipps University, Marburg, and competent health authorities were notified.

### 2.3. Outcomes

The effectiveness of rotigotine was assessed using the RLS-6. This disease-specific scale consists of 6 separate items that can be used to assess the severity profile of RLS (at bedtime, during the night, when resting during the day, and when active) in addition to sleep satisfaction and daytime sleepiness [15]. Each item is individually graded by the patient from 0 (not present/completely satisfied) to 10 (very severe/completely dissatisfied). An overall RLS-6 score generally is not calculated, as the scale has only been validated on a single-item basis [15]. In our study, primary variables were defined as change from baseline to the final visit in the severity of RLS while falling asleep (RLS-6 item 2) and the severity of RLS during the night (RLS-6 item 3) [15]. Secondary variables included satisfaction with sleep (RLS-6 item 1), severity of RLS during the day while at rest (RLS-6 item 4) and while active (RLS-6 item 5), and daytime sleepiness/tiredness (RLS-6 item 6) [15]. The usual daily start time of RLS symptoms was documented at baseline and end of treatment. Safety assessments included incidence of all adverse events (AEs) and serious AEs. A serious AE was defined as any untoward medical condition that resulted in death or was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, resulted in a congenital anomaly or birth defect, or was considered to be medically important (i.e., led to a relevant impairment of patient health or required intervention to avoid a condition that would meet the criteria of a serious AE). A post hoc assessment of rotigotine dose titration and switching practice from previous dopaminergic treatment also was performed; RLS medication at entry to the study, starting dose of rotigotine, rotigotine dose adjustments, and concomitant RLS medications were assessed. The first 4 weeks following the initiation of rotigotine were of particular interest, as it was considered that patients were likely to have reached an optimal stable dose during this time period.

### 2.4. Statistical analyses

Enrollment of 700 patients was planned over a 9-month recruitment period, with the goal of obtaining valid data from 500 patients at the end of the study. The sample size calculation was based on the primary variables (mean change from baseline in RLS-6 item 2 and item 3). All variables were analyzed in an exploratory manner using only descriptive statistics (mean, median, standard deviation, minimum and maximum values). Absolute and relative frequencies were calculated for categorical variables and summary statistics were given for continuous variables. Effectiveness analyses were performed on the full analysis set (FAS), which included patients who had not received pretreatment with rotigotine, had received rotigotine at least once during the study period, and had valid baseline scores and at least one valid postbaseline score for both RLS-6 item 2 and item 3. Safety analyses were performed on the safety set, which included all patients who received at least one dose of rotigotine. The post hoc analysis of switching practice was conducted using the FAS, and concomitant medications (approved dopaminergic premedication only) were assessed in patients with documented pretreatment for RLS beginning at least 7 days prior to the switch and evaluable dosing data.

## 3. Results

### 3.1. Patients

The study was conducted between April 2010 and July 2011. A total of 687 patients were enrolled from 101 sites (average enroll-