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Original Article

Augmentation in the treatment of restless legs syndrome with transdermal rotigotine

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ABSTRACT

Objective: To assess the risk of augmentation under treatment with the transdermally delivered dopamine agonist rotigotine for restless legs syndrome (RLS).
Methods: Experts in RLS augmentation retrospectively reviewed data from two double-blind, placebo-controlled 6-month trials (745 rotigotine and 214 placebo subjects, NCT00136045 and NCT00135993) and from two open-label 1-year trials (620 rotigotine subjects, NCT00498108 and NCT00263068). All study visits were systematically evaluated applying the Max Planck Institute (MPI) criteria for the diagnosis of both augmentation and clinically relevant augmentation.
Results: MPI criteria for augmentation were met on at least one visit by 8.2% of all subjects in the double-blind trials with 12 subjects meeting the criteria for clinically relevant augmentation: 11 under rotigotine (1.5%) and one under placebo treatment. In the open-label trials, 9.7% of all subjects met the MPI criteria for augmentation and 2.9% met the criteria for clinically relevant augmentation. None of the patients treated with rotigotine for up to 1.5 years (double-blind plus open-label trial) discontinued prematurely owing to augmentation. Neither could dose-dependency or a time pattern for clinically relevant augmentation episodes be detected.
Conclusions: Our analyses suggest that the risk for clinically relevant augmentation for the duration of up to 18 months of rotigotine treatment is low.

1. Introduction

Augmentation is the main complication of long-term dopaminergic treatment of patients with restless legs syndrome (RLS) [1]. The condition was first described in 1996 [2] and named augmentation as it involved an increase in severity of RLS symptoms after initial response to levodopa therapy. Earlier onset of symptoms is the most common feature often observed along with an increase in symptom intensity, shorter latency to onset of symptoms at rest, and expansion of symptoms from the legs to the upper limbs, trunk, and head. The clinical presentation of dopaminergic augmentation resembles the one seen in severe RLS [2,3]. This implies that none of the clinical features of dopaminergic-induced augmentation are specific to this condition or can be differentiated from RLS itself. Augmentation is not necessarily a severe complication; in many cases it can be mild without clinical or therapeutic consequences [4]. However, when augmentation is severe, the circadian pattern virtually disappears as RLS symptoms are present continuously throughout the day and are no longer relieved with activity. Frequently, particularly pronounced sleep disruptions with marked difficulties in initiating and maintaining sleep occur, and patients experience a significant reduction in their quality of life [3]. Augmentation might require a dose reduction in dopaminergic treatment, a change of dopaminergic treatment, or a combination treatment of low doses of a dopaminergic and a non-dopaminergic agent [1,5].

Augmentation has to be differentiated from early morning rebound (reappearance of symptoms in the early morning following end of dose), progressive worsening of the clinical course of RLS, and tolerance to treatment (decrease in medication effectiveness

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over time) [6]. Progressive worsening of RLS severity cannot be evaluated when patients are on drug treatment. Unlike augmentation, loss of response does not involve a worsening of symptoms to beyond the levels observed prior to initiation of therapy, and symptoms can be improved by an increase in dose. However, it can be difficult to differentiate augmentation from normal fluctuations in general RLS severity. Although, this phenomenon has been described by patients and physicians, symptom fluctuations have not yet been formally defined and no data are available from empirical studies.

In 2003, diagnostic criteria were defined which were based exclusively on clinical experience [7]. These criteria were revised in 2006 at an international consensus conference which used empirical information yielded by clinical studies [3]. These so-called "Max Planck Institute (MPI) criteria for the diagnosis of augmentation" are presented in Table 1; criteria for the definition of clinically relevant augmentation are summarized in Table 2. A rating scale specifically designed to measure augmentation severity in clinical trials (Augmentation Severity Rating Scale; ASRS) has recently been validated [8] that can be used once the condition has been diagnosed. However, the diagnosis of augmentation relies on clinical judgment and requires an experienced evaluator. For clinical trials it is recommended that a central panel of experts evaluates any available information on changes in treatment outcome over time and adjudicates the cases of augmentation.

Although augmentation seems to be particularly common during treatment with levodopa [2,9–11], it has also been observed with the dopamine agonists pramipexole [6,12–14], ropinirole [15], and cabergoline [10,16,17]. To assess the augmentation risk under the transdermally delivered dopamine agonist rotigotine,

Table 1
Max Planck criteria for augmentation [3].

Criteria	RLS rating scales used to assess augmentation criteria
Preamble	
Augmentation is a worsening of RLS symptom severity experienced by patients undergoing treatment for RLS. The RLS symptoms in general are more severe than those experienced at baseline	
A. Basic features (all of which need to be met)	
1. The increase in symptom severity was experienced on 5 out of 7 days during the previous week	Could not be evaluated with trial data
2. The increase in symptom severity is not accounted for by other factors such as a change in medical status, lifestyle or the natural progression of the disorder	IRLS sum score, RLS-6, CGI-1
3. It is assumed that there has been a prior positive response to treatment	Change in IRLS total score by at least 50% compared to baseline
In addition, either B or C or both have to be met	
B. Persisting (although not immediate) paradoxical response to treatment	
RLS symptom severity increases some time after a dose increase, and improves some time after a dose decrease	For open-label trials only. Evaluation of rotigotine dose changes up to the maximum rotigotine dose of 3 mg/24 h in comparison to subsequent changes in intensity of symptom severity and quality of life
Or	
C. Earlier onset of symptoms	
1. An earlier onset by at least 4 h	ASRS item 1
Or	
2. An earlier onset (between 2 and 4 h) occurs with one of the following compared to symptom status before treatment	ASRS item 1
a. Shorter latency to symptoms when at rest	ASRS item 3a
b. Extension of symptoms to other body parts	ASRS item 4
c. Intensity of symptoms is greater (or increase in PLM if measured by polysomnography [PSG] or the suggested immobilization test [SIT])	ASRS item 2
d. Duration of relief from treatment is shorter	Could not be evaluated with trial data
Augmentation requires criteria A + B, A + C or A + B + C to be met	

ASRS, Augmentation Severity Rating Scale; CGI, Clinical Global Impression; IRLS, International Restless Legs Syndrome Severity rating scale; PLM, periodic limb movements; RLS, restless legs syndrome.

Table 2
Clinical augmentation severity categories according to Max Planck criteria [3].

Criteria	Assessment methods
I: Clinically significant augmentation	
Augmentation is clinically significant when at least one of the following occurs:	
a. Change in daily activities and/or behavior (e.g., the patient stops riding in cars in the afternoon) due to augmentation	Could not be assessed.
b. Negative impact on the patient's quality of life (sleep, mood, etc.) due to augmentation	RLS-QoL
c. Need to change the treatment dose or the patient needs to take the dose earlier in the day (e.g., dividing the dose)	Any dose adjustment during the open-label studies
d. Adjustments in concomitant medication are made to compensate for augmented RLS symptoms (e.g., an increased intake of analgesics or hypnotics to cover an increase in symptom intensity)	Any changes in concomitant medication during the open-label studies
e. Any other aspect as judged by the evaluator (should be specified)	
II: Not clinically significant augmentation	
None of the above mentioned criteria (a–e) are met	

RLS-QoL, restless legs syndrome quality of life.