Loss of response during long-term treatment of restless legs syndrome: Guidelines approved by the International Restless Legs Syndrome Study Group for use in clinical trials

Loss of efficacy represents a potential major problem during long-term treatment of restless legs syndrome (RLS). One retrospective study reported that 46% of patients treated with pramipexole experienced a reduced benefit of this agent over time [1]. During long-term treatment of RLS, reduction or complete loss of efficacy can occur for two main reasons: loss of response or augmentation. Loss of response, unlike augmentation, does not require RLS symptoms to become worse than before treatment, neither additional “new” RLS symptoms (e.g., a spread of symptoms to previously unaffected body parts) nor a shorter latency to symptoms at rest or an increased symptom intensity when present [2].

Any reduction of therapeutic response of RLS treatment deserves attention not only as a problem per se for long-term management, but also due to the possibility that it may be an early indicator for developing RLS augmentation because, in some cases, augmentation might go through an initial stage of tolerance. Such a progressive loss of therapeutic response in the absence of any change in metabolism of the drug could reflect a process exacerbating the underlying disease process eventually leading to augmentation. Thus, conditions that exacerbate RLS severity, such as iron deficiency [3] or concomitant treatment with SSRIs [4], might mimic augmentation. On the other hand, during augmentation there is an iatrogenic change in RLS pathophysiology whereby drugs which previously exerted a therapeutic effect might not only now lose any therapeutic action, but even exacerbate symptom severity.

We, as a group of international RLS experts, while evaluating RLS augmentation in clinical trials, have recognized the need to also define loss of response during these trials. Since there is no current standard for identification of loss of response in clinical trials we have developed one such standard (Table), which has been approved by the International Restless Legs Study Group (IRLSSG).

Definition of loss of clinically relevant response for clinical trials

A loss of response occurs when the patient meets both of the following two criteria:

**Criterion A (defines initial clinically relevant response):**
During the first three months of treatment, on any two consecutive evaluations at least one week apart:

1) there is a reduction in the IRLS total score by ≥40% from the baseline value, i.e. IRLS ≤ 60% of the baseline value. (Example 1: a baseline IRLS score of 25 with decreases after treatment to ≤15);

or

2) the IRLS score ≤ 10 (Example 2: regardless of the initial score, there is an improvement to ≤ 10)

**Criterion B (defines clinically relevant loss of initial response):**
Once clinically relevant response is established according to Criterion A, loss of response is defined as follows:

1) on any two consecutive evaluations at least one month apart, there is an increase of the IRLS score to > 70% of the baseline score (Example 1: baseline IRLS score of 25, treatment response of IRLS ≤ 15 followed by worsening with IRLS increased on two visits to ≥ 18) and there is no re-establishment of response (defined as criterion A) afterwards without a dose increase.

or

2) a dose increase occurring:

- after the first 3 months of treatment

  or

- within the first 3 months of treatment and preceded by one evaluation with IRLS >70% of baseline

3) The patient drops out due to loss of response as determined by the investigator

If the patient meets both criteria A and B indicating loss of response, the investigator should determine the presence of augmentation. The patient should be classified as one of the following:

- Loss of response with augmentation
- Loss of response without augmentation
- Loss of response – augmentation state not assessed

Disclosures

D. Garcia-Borreguero has been a consultant and speaker for GlaxoSmithKline, Pfizer, Boehringer Ingelheim, UCB, Jazz Pharma, MSD, Sanofi-Aventis, Otsuka and Lundbeck. He has served as an expert consultant in the evaluation of long-term clinical trials on ropinirole, pramipexole, rotigotine, lisuride, and pregabalin.

R. Allen has served as a consultant for Boehringer Ingelheim, GlaxoSmithKline, Luitpold Pharmaceuticals, Pfizer, EMD Serono, Pharmacosmos, and UCB Pharma. He has received research support from GlaxoSmithKline and the USA National Institutes of Health. He has served as an expert consultant in the evaluation of long-term clinical trials on ropinirole and pregabalin.

R. Kohnen has served as a consultant and member of advisory boards for Axononis Pharma, Jazzpharma, Mundipharma, Roche, Pfizer, and UCB Pharma. He has served as an expert consultant in the evaluation of long-term clinical trials on cabergoline, levodopa, lisuride, oxycodone/naloxone, pregabalin, and rotigotine.

H. Benes has received honoraria from UCB, GlaxoSmithKline and Boehringer Ingelheim for consultancy, membership in advisory boards, and as a lecturer. She has served as an expert consultant in the evaluation of long-term clinical trials on rotigotine.

B. Högl has received honoraria from UCB, Boehringer Ingelheim, GlaxoSmithKline, Cephalon, Pfizer, and Sanofi for consultancy.
membership in advisory boards, and for lectures. She has served as an expert consultant in the evaluation of long-term clinical trials on ropinirole, pramipexole and rotigotine.

J. Winkelmann has received research support from GlaxoSmithKline and honoraria from GlaxoSmithKline, Impax Pharmaceuticals, Pfizer and UCB. He has served as an expert consultant in the evaluation of long-term clinical trials on ropinirole and pregabaline.

L. Ferini-Strambi has served on scientific advisory boards for Boehringer Ingelheim, GlaxoSmithKline, Sanofi-Aventis and UCB Pharma. He has served as an expert consultant in the evaluation of long-term clinical trials on ropinirole, pramipexole and rotigotine.

M. Zucconi has served as an expert consultant in the evaluation of long-term clinical trials on lisuride.

C. Trenkwalder received honoraria from UCB, Boehringer Ingelheim, Cephalon, Novartis and Solvay for consultancy, membership in advisory boards, and as lecturer. She served as an expert consultant in the evaluation of long-term clinical trials on pramipexole and rotigotine.

Acknowledgment

To Anne-Marie Williams for her important editorial help.

References


Sodium oxybate and modafinil: A good combination?

To the Editor,

We read carefully the papers published by Rossetti et al. [1] and Zvosec et al. [2], and we agree that psychiatric alterations should be considered in patients under combined treatment with sodium oxybate (SO) and modafinil. We treated 27 patients with SO, and 13 of them also had modafinil (100–150 mg/day). Seven of these 13 developed psychiatric symptoms without previous history: three with anxiety and four with mixed anxiety–depressive disorder. One of the patients developed suicidal ideation. This case was reported to the Spanish Drug Safety System (Register number 15690).

It is notable that five of the seven who developed psychiatric side effects were under modafinil treatment previously, most of them with higher doses. In our patients there was a temporal relationship between the onset of new symptoms and ingestion of SO or modafinil. Four patients after modafinil withdrawal, two patients after SO withdrawal, and one patient after reduction of SO (from 6 to 4 g) remained free of psychiatric symptoms.

In conclusion, physicians should carefully monitor for psychiatric alterations in narcolepsy–cataplexy patients treated with SO and CNS stimulant drugs.

References


C. Trenkwalder
Paracelsus-Elena Hospital,
Center of Parkinsonism and Movement Disorders,
Kassel, Germany

J.J. Ortega-Albás
Sleep Unit, General Hospital of Castellón,
Avenida Benicasim s/n, 12004 Castellón de la Plana, Spain
* Address: Avenida de Capuchinos 41,
2º D, 12004 Castellón, Spain.
Tel.: +34 638713784.
E-mail addresses: joral@on.com

R. López-Bernabé
Clinical Neurophysiology Service,
Santa María del Rosell Hospital,
Paseo Alfonso XIII 61, 03020 Cartagena, Spain

J.R. Serrano
Clinical Neurophysiology Service,
General Hospital of Castellón,
Avenida Benicasim s/n, 12004 Castellón de la Plana, Spain

J.J. Ortega-Albás
Sleep Unit, General Hospital of Castellón,
Avenida Benicasim s/n, 12004 Castellón de la Plana, Spain

J.R. Díaz
Sleep Unit, General Hospital of Castellón,
Avenida Benicasim s/n, 12004 Castellón de la Plana, Spain