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CURRENT OPINION

Long-Term Treatment of Restless Legs Syndrome (RLS): An Approach to Management of Worsening Symptoms, Loss of Efficacy, and Augmentation

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Abstract Restless legs syndrome (RLS) is a common, frequently chronic, sensorimotor neurological disorder characterized by nocturnal leg dysesthesias and an irresistible urge to move the legs, usually resulting in sleep disturbance. Dopaminergic agonists, alpha-2-delta calcium-channel ligands, and opioids have all demonstrated efficacy to relieve symptoms of RLS and improve sleep. However, long-term treatment with dopamine agonists (the most commonly prescribed agents) is often characterized by worsening symptoms and loss of efficacy. A more worrisome complication of dopaminergic agents is augmentation, an iatrogenic worsening of RLS symptoms that can produce progressively more severe symptoms resulting in around-the-clock restlessness and near sleeplessness. Recent research has yielded consensus regarding a precise definition of augmentation and has contributed to improved knowledge regarding strategies for preventing this complication. When RLS symptoms worsen during the course of treatment, the clinician must consider the myriad of environmental, medical, pharmacologic, and psychiatric factors that can exacerbate RLS. In the absence of fully developed, evidence-based guidelines there remains uncertainty regarding the optimal management strategy if augmentation develops. However, we discuss several key principles based on the available published data and the authors' clinical experience. We also explore the recent increasing interest in alternative initial treatment strategies that avoid dopamine agonists and their associated complications altogether.

Key Points

Restless legs syndrome (RLS) is a common sleep disorder for which several effective treatments are available.

Because RLS is often a lifelong disorder, the clinician should be aware of the most common reasons for worsening symptoms and loss of efficacy during treatment.

Long-term treatment with dopaminergic agents can lead to augmentation, an iatrogenic worsening of symptoms which may require a change in treatment strategy.

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1 Introduction

Restless legs syndrome (RLS) is a common sensorimotor sleep disorder. Approximately 2–3 % of the population suffer from clinically significant symptoms that confer adverse effects on sleep, quality of life, and health [1]. RLS is characterized by an irresistible urge to move the legs, often paired with leg dysesthesias. Symptoms are provoked

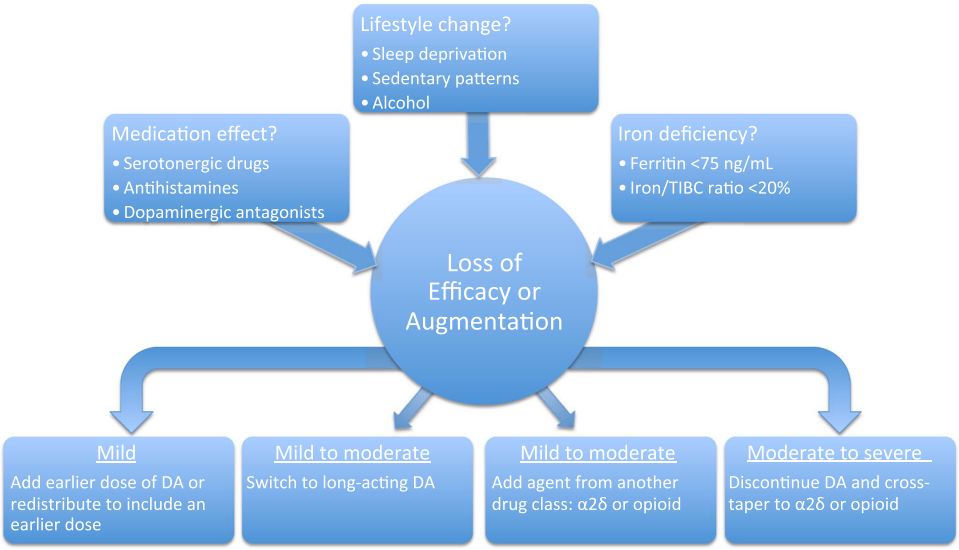

Fig. 1 Management of worsening RLS symptoms, loss of efficacy, and augmentation. *DA* dopamine agonist, *α2δ* alpha2-delta agent, *RLS* restless legs syndrome

by rest, relieved with movement, and are most prominent in the evening or at night [2, 3]. RLS is often a lifelong condition requiring long-term treatment. In recent years, clinical and research experience in RLS has witnessed the complexity of extending short-term treatment strategies for long-term management [4]. The aim of this article is to provide an overview of available RLS treatment options and a strategy for addressing RLS symptoms that re-emerge or worsen during long-term treatment (Fig. 1). Due to the lack of rigorous data or firm consensus guidelines, the suggestions herein reflect the authors' opinions based on our clinical experience and the limited available data.

2 Drug Treatment: An Overview of Available Options

Several classes of drugs are effective for the treatment of RLS. At present, dopaminergic agents are usually the first-line of treatment [4, 5], and pramipexole and ropinirole (as well as levodopa in Europe) are the most frequently used oral agents. Ropinirole has a faster onset of action than pramipexole (time to reach maximum concentration [t_{max}] = 1 vs. 2 h for pramipexole) but a somewhat shorter duration of action (terminal half-life ~6 h vs. 8–12 h for pramipexole). Doses are generally timed to precede usual symptom onset by 1–2 h. Rotigotine is a dopamine agonist formulated as a transdermal patch for daily application. Its continuous delivery system provides stable plasma concentrations around-the-clock, making this agent particularly useful for treating patients with symptoms throughout the day.

Alpha-2-delta agonists such as gabapentin, gabapentin enacarbil, and pregabalin have also gained acceptance as possible first-line agents for RLS. A recent double-blind study comparing pregabalin, pramipexole, and placebo over a 12-week period, and the two active agents over a 52-week treatment period, demonstrated efficacy of pregabalin that was superior to placebo and comparable with the dopamine agonist [6]. Such data indicate that the first-line use of alpha-2-delta agents may become more accepted going forward.

Opioids are a third class of drugs with demonstrated efficacy for RLS. These are not commonly employed as initial treatments of choice due to concerns regarding abuse potential and side effects such as respiratory depression and constipation. However, a recent randomized, double-blind trial demonstrated the efficacy of an extended-release oxycodone–naloxone combination to achieve impressive and persistent improvement of RLS symptoms in patients who had not benefited from first-line agents [1, 7]. In addition, there is observational evidence that low-dose methadone can be effective at stable doses for long-term management [8, 9].

When selecting a medication to initiate treatment for RLS, the clinician should keep in mind the most common long-term side effects specific to each class of drug [4]. Dopamine agonists may cause sleepiness in some patients, which can be a problem for those requiring treatment during the daytime. Impulse control disorders (ICDs) such as compulsive gambling or binge eating are also occasionally associated with these drugs. All patients should be warned about the possibility of ICDs prior to starting a dopamine agonist; this class of drugs is relatively contraindicated in those with a history of ICDs. Alpha-2-delta agents may cause weight gain during long-term treatment and should be avoided in patients attempting to lose weight. Another common side effect is dizziness or gait instability. Finally, opioid medications may be associated with misuse or

diversion in some patients, and caution should be taken when prescribing these for patients with a history of substance abuse. Methadone, an opioid commonly used in the US (but not elsewhere) for RLS, has been associated with decreased testosterone levels, which may manifest as decreased libido, depression, apathy, or night sweats.

3 Assessment and Management of Re-Emergent or Worsening Restless Legs Syndrome (RLS) Symptoms During Long-Term Treatment

Despite initial improvement of symptoms, it is common for the clinician to encounter re-emergent or worsening RLS symptoms in a patient undergoing treatment. Tzonova et al. performed a cross-sectional survey among patients receiving drug treatment for RLS, and found that 41 % suffered persistent daytime symptoms on a daily basis [4, 5, 10]. In addition, worsening night-time symptoms are commonly observed [6, 11]. When a clinician encounters new or worsening RLS symptoms despite treatment, he/she should first inquire about changes in the patient's lifestyle or health that could account for this deterioration. Such factors are important to identify because they may be reversible and unnecessary changes in the existing medication regimen can thus be avoided.

3.1 Is the Patient More Sedentary?

RLS is, by definition, provoked by rest and improved with movement. A patient who transitions from a more active lifestyle to more stationary patterns (e.g. as a result of changing jobs, retirement, depression, comorbid medical conditions, or simply personal choice) may experience worsening of RLS symptoms. Alerting the patient to the association between immobility and the severity of RLS symptoms may be adequate. If not, the clinician should strategize with the patient about ways to increase activity, emphasizing that the primary focus of treatment will be nocturnal, sleep-disruptive symptoms.

3.2 Is the Patient Sleep-Deprived?

Sleep deprivation exacerbates RLS symptoms [12]. A patient who takes on a new job working long hours, or a patient who voluntarily restricts sleep time as a lifestyle choice, may show new or worsening RLS symptoms during the course of treatment as a result of their sleep-deprived state. A sleep diary that records both sleep patterns and RLS symptoms may be a useful tool in helping a patient gain insight into this association. Although all patients should be counseled to allow adequate time for sleep, this advice is especially crucial for RLS patients.

In addition to lifestyle changes, other sleep disorders are a common cause of sleep deprivation. Sleep disturbance is prevalent in RLS patients and may create a vicious cycle of sleep deprivation, resulting in worsening RLS symptoms that, in turn, cause further sleep loss. As a result of long-standing, untreated RLS, such patients have been shown to share, with primary insomnia patients, dysfunctional attitudes about sleep that may also play a role in perpetuating insomnia [13]. Obstructive sleep apnea (OSA) should also be considered if there are suggestive indicators such as excessive daytime sleepiness, loud snoring, or witnessed apneas. Diagnosis and treatment of OSA with nocturnal positive pressure can alleviate both OSA symptoms and repercussions the condition may have for RLS.

3.3 Are Comorbidities Influencing Symptoms?

RLS shares many features of chronic pain disorders, including the tendency to be exacerbated by concomitant psychiatric and medical conditions. Psychiatric conditions in particular are highly prevalent among RLS patients. The lifetime prevalence of depression (major depressive disorder [MDD] or dysthymia) has been reported to be 37 % in RLS patients versus 15 % in a control group [14]. As depression is associated with immobility due to excessive time lying in bed, low energy, psychomotor retardation, or social avoidance, the mood disturbance may predispose to RLS symptoms. In addition to pharmacologic treatments directed towards the mood disorder, cognitive behavioral methods directed towards coping with the chronic illness of RLS are encouraged [15].

3.4 Are There Pharmacologic Factors Exacerbating RLS?

Although poorly recognized, many common classes of drugs can exacerbate RLS. Combination antihistamine/anticholinergic agents such as diphenhydramine are a popular class of over-the-counter agents that exacerbate RLS [16]. These may be taken by uninformed RLS patients in a counterproductive effort to improve sleep. Similarly, dopaminergic antagonistic antiemetics or antipsychotics are commonly used in clinical practice and can worsen RLS [17]. Simply alerting the patient to the adverse effects of these agents is often sufficient.

Given the prevalence of MDD and anxiety disorders in RLS patients, the prescription of antidepressants is common. Unfortunately, these medications with serotonergic and/or antihistaminergic activity (selective serotonin reuptake inhibitors [SSRIs], mirtazapine, tricyclic antidepressants) can worsen RLS [18]. A dose reduction may be sufficient to alleviate RLS symptoms, or, alternatively, a different class of antidepressant could be considered.

Bupropion is an effective antidepressant that has not been shown to contribute to RLS symptoms, and may be a good choice in such patients [19].

Medication withdrawal may also contribute to RLS. Most dramatically, tapering or stopping chronic opioids (either therapeutic or recreational) is likely to trigger worsening of symptoms in an RLS patient [20], an effect that is often temporary. If such a decrease in opioids is otherwise desirable, a patient may be counseled accordingly, and temporary use of a dopaminergic agent may be appropriate.

In addition to therapeutic agents, in our clinical experience recreational alcohol use commonly worsens RLS symptoms. Patients with unexplained worsening of symptoms should be questioned regarding alcohol intake. Both healthy and disordered use may contribute, and cutting back or eliminating this intake may provide substantial benefit.

3.5 Is the Patient Iron Deficient?

Iron deficiency has a clear association with RLS, although the pathophysiology is not well understood [21]. Both at the time of diagnosis and when addressing an unexpected deterioration in treatment efficacy, iron studies should be obtained [4, 22]. In addition to serum ferritin, iron and total iron-binding capacity (TIBC) should also be tested because ferritin can be falsely elevated in patients with chronic inflammatory conditions [23]. Iron supplementation has been shown to reduce RLS symptoms even in patients with low–normal ferritin [24]. Patients should be prescribed oral ferrous sulfate supplementation to achieve ferritin >50 ng/mL. The transferrin saturation (ratio of iron to TIBC) should be maintained at >20 %. Other than menstruating women, those who are found to be iron deficient should also be referred for medical evaluation to determine the underlying cause of iron deficiency.

3.6 Loss of Efficacy and Augmentation

If none of the above lines of inquiry yields fruitful strategies for addressing worsening or re-emergent RLS symptoms, the clinician should consider whether the patient is experiencing loss of efficacy (i.e. 'tolerance') or augmentation. The worsening of RLS symptoms seen in these two processes may be the result of the natural history of RLS worsening over time or a CNS compensatory response to chronic drug treatment, a distinction that may be difficult to make in an individual patient. However, when the degree of symptom severity exceeds that observed prior to the initiation of drug treatment, it is prudent to consider that it is iatrogenic.

Loss of efficacy refers to the reappearance of RLS symptoms, which are similar (in severity, timing, and anatomic distribution) to those prior to treatment, after an initial positive response to treatment that is not explained by extenuating factors such as those outlined above [11, 25].

A related, but more worrisome complication than loss of efficacy is augmentation, an iatrogenic worsening of RLS symptoms that occurs because of drug treatment. It is seen almost exclusively during treatment with dopaminergic agents. Augmentation is usually manifested as an earlier onset of symptoms than was present before initiation of medication treatment. An increased intensity of symptoms, shorter latency to symptom onset with immobility, reduced duration of treatment effect, and involvement of previously unaffected limbs can also be observed [26]. For a diagnosis of augmentation to be made, symptoms must be present for at least 5 days over at least a 1-week period, and they must not be explained by other behavioral or pharmacologic factors (such as those described above).

Augmentation manifests clinically along a continuum of severity, which is thought to depend on the duration and dose of dopaminergic treatment as well as individual factors, including iron deficiency [4, 27]. Although earlier administration of medication or increases in dose will often temporarily relieve RLS symptoms in the augmented patient, progressive augmentation may occur. This often includes earlier and earlier temporal onset, continued shortening of the duration of medication benefit, and increasingly severe symptoms, any of which may stimulate the clinician to again increase the dose, further stimulating the augmentation process.

In addition to the dose and duration of use of the dopaminergic agent, shorter-acting agents in this class are associated with greater rates of augmentation. However, most randomized controlled trials in RLS have thus far been relatively short in duration, therefore assessment of augmentation rates is limited. Nevertheless, augmentation risk appears to be highest with shorter-acting agents such as levodopa, where it occurred in 60–80 % of patients receiving treatment [28, 29]. Ropinirole and pramipexole have lower rates of augmentation. In one short trial using pramipexole, the 6-month incidence of augmentation was 9.2 % for pramipexole compared with 6.0 % for placebo [30]. Observational data spanning longer time periods have generally demonstrated a higher incidence of augmentation with these agents. For instance, augmentation was seen in approximately one-third to one-half of patients receiving pramipexole, after 2–8 years of treatment [11, 31, 32]. In a cross-sectional, community-based survey of patients receiving various dopaminergic agents, 20 % of patients were classified as having definitive or highly suggestive indicators of augmentation. Only 25 % of patients reported

no indicators of augmentation [33]. It is unclear whether the continuous transdermal delivery system employed by the rotigotine patch has a lower likelihood of causing augmentation [34].

4 Strategies to Prevent Augmentation

The initial choice of drug is an important decision that will affect the likelihood of augmentation. The remarkable efficacy of dopaminergic agents must be weighed against their potential to provoke augmentation. In patients with milder symptoms, starting with a trial of an alpha-2-delta agent to prevent or delay the introduction of a dopaminergic may be desirable. Other recommended factors influencing the initial treatment choice are described in a recent consensus report [4]. Levodopa should only be used for PRN use (e.g. plane flights, car rides, theatre, etc).

During the course of treatment, it is common for patients to require gradually increased doses of a dopamine agonist [11, 32, 33]; however, because the risk of augmentation probably rises with increasing doses, the clinician should be careful to use the lowest effective dose. That being said, establishing the lowest effective dose can be difficult in a disorder characterized by substantial daily fluctuations in symptom severity, particularly when medication is timed to precede symptom onset. Adding a non-dopaminergic agent as a combined management strategy is often employed as an appropriate alternative to increasing the dopaminergic agonist dose.

It is the experience of these authors that RLS patients may develop some of the dysfunctional attitudes about RLS symptoms that insomnia patients have about sleep, chronic pain patients have about pain, and those with panic disorder have about panic attacks. Such anticipatory anxiety about RLS symptoms may compel patients to administer dopamine agonist medication earlier and to take higher doses than would otherwise be required. The vigilant clinician should take care to make specific plans with the patient regarding appropriate medication dosing and the value of behavioral approaches to symptom management, particularly during the day, when mobility is feasible. Alerting patients to the counterproductive effects of excessive 'pill popping' can thus help to involve the patient in a treatment plan that minimizes the risk of augmentation.

5 Strategies to Address Augmentation

If augmentation is identified by a generalist, referral to a sleep medicine specialist for assistance with management is appropriate where available. The optimal strategy for augmentation remains to be fully elucidated, but several reasonable options are available. First, one can 'chase' RLS symptoms by adding an earlier dose or redistributing the same dose earlier. This approach is appropriate for patients taking relatively low doses of a dopamine agonist when augmentation emerges, and for those in whom augmented symptoms are mild to moderate and remain localized into the evening and night-time. If the total daily dose is increased, the clinician should be vigilant to the possibility of progressive augmentation that may be further provoked by dose increases. For patients who regularly develop symptoms during the day, switching to a long-acting dopamine agonist formulation such as transdermal rotigotine or extended-release formulations of pramipexole [35] or ropinirole may be a more appropriate approach, as long as doses of these medications are kept within the approved range for RLS.

In addition to, or as an alternative to, increasing the dose of dopamine agonists, the addition of a non-dopaminergic agent may be a helpful strategy in addressing mild augmentation and in keeping the dopaminergic dose low. Gabapentin, gabapentin enacarbil, or pregabalin are often used. In some cases, a low-dose opioid could be an appropriate alternative.

For patients receiving higher doses of dopamine agonists when augmentation appears, or for those who have already been through one or more dose escalations to address augmentation, minimization or discontinuation of the dopaminergic agent is usually necessary. Unfortunately, dose reductions of dopaminergic agents often produce an increase in RLS symptom severity, at least temporarily, which can be quite dramatic and distressing and can lead to severe insomnia. Therefore, gradual dose reduction of the dopaminergic agent is best achieved after establishing an effective dose of another agent (such that the patient is temporarily taking two agents). In such situations, a long-acting opioid (e.g. methadone, extended-release oxycodone) is often the treatment of choice, although an alpha-2-delta agent may also be useful.

6 Future Directions and Conclusions

Despite considerable attention in recent years dedicated to understanding the prevalence and risk factors for augmentation, there remains a dearth of controlled studies to provide guidance regarding optimal management of this iatrogenic complication of dopaminergic agents. The strategies outlined above have been developed through the combined clinical expertise of practitioners caring for these patients. However, the decision regarding when to discontinue dopaminergic agents during the course of managing augmentation varies between clinicians, and further research is needed to determine the ideal approach.

Also uncertain is whether some, or most, RLS patients would be better managed without the initial introduction of a dopaminergic drug. As discussed above, recent evidence has demonstrated the efficacy of pregabalin as an alternative to dopaminergic agents for at least 1 year; however, the majority of clinicians still prescribe a dopaminergic agent at the time of diagnosis. Rigorous randomized studies of long-term treatment are needed to determine what initial strategy is most suited to alleviate symptoms throughout the course of this frequently chronic illness.

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