symptoms begin to occur at least 2 hours earlier in the day. These symptoms may become more intense, may spread to other body parts (especially the arms, but expansion to all other body parts including the face is possible), and the time at rest before symptoms occur may significantly decrease. In addition, the previous dose of medication may not be as effective in decreasing symptoms or last as long. Increasing the dose may help at first, then become less effective and may lead to further augmentation symptoms. Stopping the medication will typically result in a marked increase in symptoms followed by a return to pretreatment levels after a few weeks.

Symptoms must be present for at least 1 week and a minimum of 5 days per week before augmentation can be diagnosed.[33] The onset of symptoms can be as soon as 1 week but typically occurs within 2 months when due to L-dopa[33] and 6 to 9 months[33,37] with dopamine agonists, but can also be delayed by many years with dopamine agonists.

Augmentation must be differentiated from situations that may appear somewhat similar (**Table 9.6**). As RLS tends to worsen slowly with time, one must be sure that the worsening of symptoms is not due to disease progression. This can be difficult at times as the disease may progress in an erratic fashion and the onset of augmentation may be delayed by many years. At times, the only way to decide if augmentation exists is to stop the dopamine drug and see if symptoms revert to where they were prior to treatment (which does not occur with disease progression).

TABLE 9.6 — Differential Diagnosis of Augmentation

- Natural disease progression of RLS
- Rebound
- Tolerance
- Worsening of RLS due to other factors

Initially, rebound may be confused with augmentation in that patients complain about a worsening of symptoms despite therapy. However, rebound occurs at the end of the dose as a late effect while augmentation presents as an earlier onset of symptoms.

Tolerance shares some of the features of augmentation in that the drug effect diminishes; higher doses are needed to treat symptoms and drug responsiveness usually returns after a few weeks off the drug. Due to these similarities, it has been suggested that tolerance may in fact be a subtype of augmentation[37] caused by a similar downregulation of dopamine receptors. However, for diagnostic purposes, tolerance does not result in an earlier onset of RLS symptoms or expansion of symptoms to other body parts.

Worsening of symptoms due to other causes must also be ruled out. Medications (antihistamines, psychiatric medication, etc), iron deficiency, sleep deprivation, alcohol use, and vigorous exercise are among the many different causes that may exacerbate RLS. Before diagnosing augmentation, doctors should search for exacerbating factors. If the worsened RLS symptoms can be linked to one of these extrinsic factors, symptoms may be improved by simply correcting the offending cause.

Treating Augmentation

Although the daily use of L-dopa has decreased considerably so that L-dopa augmentation does not occur as often as in the past, it is still being prescribed on a daily basis in significant quantities. Augmentation that occurs due to L-dopa therapy usually results in very severe RLS symptoms and should be addressed as soon as possible. The medication should be stopped and replacement therapy with a dopamine agonist or other class of medication should be instituted. However, this must be done carefully as RLS symptoms usually dramatically worsen when L-dopa is withdrawn in this setting. Often an opioid may be necessary for breakthrough RLS symptoms until the new therapy reaches therapeutic levels. If a dopamine

agonist is used as replacement therapy, it can be titrated up as the L-dopa is weaned down. There is some controversy about replacing one dopaminergic drug with another due to the concern of recurrent augmentation and physicians should be vigilant for its reemergence.

With the decreased use of L-dopa, augmentation with dopamine agonists is now more common in clinical practice. Mild augmentation where symptoms increase mildly and just occur a few hours earlier may be treated by giving the dopamine agonist dose earlier (and possibly increasing the dose modestly) or by giving two split doses with the first dose timed 1 to 2 hours before symptoms. Alternatively, a longer-acting dopamine agonist like the rotigotine patch or even a change to a different short-acting dopamine agonist may be helpful. As described above with L-dopa, replacing one dopaminergic drug with another might cause recurrent augmentation and physicians should be very vigilant for its reemergence. Drug levels should be kept as low as possible and the need for higher doses should alert the physician to the likelihood of worsening augmentation.

Treating severe augmentation is much more difficult and controversial. Many RLS experts believe that the dopamine agonist should be discontinued completely while others suggest that it may be reduced to lower levels. There are no studies evaluating any technique to handle augmentation, so therapy is based on clinical experience. Adding increased doses of dopamine agonists to a patient with severe augmentation (which is what is done by most physicians including specialists who are not RLS experts) will provide temporary relief but will eventually add "fuel to the fire" and cause even worsened symptoms that will perpetuate the vicious cycle of augmentation that demands yet higher doses. Thus, the dopamine agonist must be stopped or decreased.

Whether dopamine agonist doses are abruptly eliminated, tapered off slowly, or reduced to lower levels, RLS symptoms will be dramatically increased over their current worsened state. With no additional

treatment, patients may improve (possibly even a marked improvement to minimal or no symptoms) slowly over a few months but the transition period will typically be a hellish experience. Anticonvulsant drugs (α2δ ligands) may mitigate some of these symptoms but usually are not effective enough for this situation.

Most patients will need a potent opioid (methadone, oxycodone) to treat the dramatically worsened RLS symptoms created by the withdrawal of their dopamine agonist. Physicians who are unwilling or unable to prescribe potent opioids for these patients when other options fail should refer them to another physician. The opioid may need to be prescribed up to three times daily to cover the around-the-clock RLS symptoms that ensue upon reducing or withdrawing dopamine agonists. After a few weeks, the dose of opioids may be gradually reduced as RLS symptoms typically abate somewhat. After a few months, adding an α2δ ligand may be offered to the patient in order to further reduce or eliminate the need for opioids. Patients may end up on opioid monotherapy, a low dose of an opioid, and an α2δ ligand, or a low dose of a dopamine agonist, an α2δ ligand, and an opioid. Treatment should be individualized to the level of RLS symptoms, side effects of treatment, and needs of the patient as is discussed in *Chapter 10*.

Measures that may prevent augmentation from occurring in the first place are keeping the dopamine agonist dose as low as possible, choosing longer-acting dopamine agonists, and keeping serum ferritin levels high (as lower ferritin levels have been associated with increased augmentation[46,47]).

Unapproved Dopamine Agonists for Treating RLS

This next group of drugs consists of older dopamine agonists that have been used for RLS and newer ones that are under investigation. The older dopamine agonists may never be FDA approved for RLS due to side effects or because most are already off patent.

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Clinical Management of Restless Legs Syndrome

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