AUGMENTATION SUFFERING AND WHAT CAN BE DONE ABOUT IT

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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

Susan Mackie[1] · John W. Winkelman[2,3]

WHITE PAPER
SUMMARY OF RECOMMENDATIONS FOR THE PREVENTION AND TREATMENT OF RLS/WED AUGMENTATION
A COMBINED TASK FORCE OF THE IRLSSG, EURLSSG AND THE RLS-FOUNDATION

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AUGMENTATION

Augmentation is a long-term (6 months-years) complication of RLS treatment with dopaminergic medications

Dopaminergic (DA) medications:

- Levodopa (Sinemet)
- Pramipexole (Mirapex)
- Ropinirole (Requip)
- Rotigotine (Neupro)

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AUGMENTATION DEFINITION

Compared to before medication was initiated there is:

- Advance in the time of symptom onset
- More intense symptoms
- Symptoms start faster after lying down/sitting
- Extension of symptoms to arms

In short, RLS gets worse with medication treatment!

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AUGMENTATION SEVERITY EXISTS ALONG A CONTINUUM

Pre-augmentation/tolerance: DA medication dose needs to be increased to maintain effectiveness but there is no change in timing of symptoms

Mild: 2-4 hour advance in time of RLS symptom onset, most days

Severe: 4-8 hour advance in the time of RLS symptom onset, most days

Very severe: RLS symptoms present much of the day and night

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WHAT WORSENS RLS BUT ISN'T AUGMENTATION

Iron deficiency

Medication effects

- Antidepressants
- Antihistamines
- Dopamine blockers (anti-nausea or antipsychotics)

Sleep disruption/deprivation (eg sleep apnea, insomnia)

More time spent immobile (in bed, sitting, etc)

Worsening of RLS due to aging

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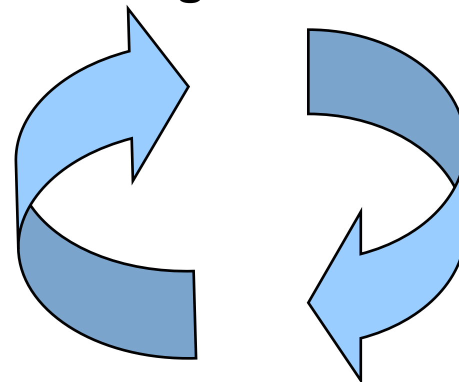
MANY DOCTORS INCREASE THE DA DOSE WHEN RLS SYMPTOMS WORSEN

But…that is often just a temporary fix

Because augmentation continues and in fact…is more likely with higher doses of DA medications

As a result, more severe augmentation usually takes place in people with higher DA doses

RLS worsening due to augmentation



Increased DA doses

WHAT TO DO ABOUT AUGMENTATION

Address any RLS-worsening factors:

Iron deficiency (keep ferritin>50)

- Supplement with $FeSO_4$ 325 mg twice per day with Vit C

Medication effects

- Antidepressants (use bupropion instead)
- Antihistamines (use nasal steroids instead)
- Dopamine blockers (substitute to a different non-dopamine med)

Sleep disruption/deprivation (eg sleep apnea, insomnia)

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3 CLASSES OF MEDICATIONS WORK FOR RLS

Dopaminergic medications

Alpha 2 delta medications

- Gabapentin enacarbil (Horizant)
- Gabapentin (Neurontin)
- Pregabalin (Lyrica)

Opiate medications

- Oxycodone, Oxycontin, Hydrocodone, Methadone

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WHAT TO DO ABOUT AUGMENTATION

Since there are only 3 classes of medications that work for RLS, there are not that many choices:

1) Readjust, increase or change DA medications
2) Switch to an alpha 2 delta medication
3) Switch to an opiate

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MILD AUGMENTATION

DA medication can be given earlier (eg move from 10pm to 6pm), split dose (eg half dose at 6pm and 10pm), or the total dose can be increased

Switch to a longer half-life DA medication (eg to rotigotine or pramipexole ER)

Add another medication (alpha 2 delta or opiate) and reduce the DA dose

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MODERATE/SEVERE AUGMENTATION

DA medication should be discontinued and switched to alpha 2 delta or opiate

However, stopping DA usually produces severe RLS symptoms for days-weeks

For this reason, recommend establishing an effective dose of the new medication before slowly tapering the DA (over weeks-months)

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Augmentation Treatment Algorithm

Eliminate exacerbating factors
(serum ferritin < 50-75 µg/mL], lifestyle changes, exacerbating drugs)

Mild augmentation

Keep the same dopamine agonist

One of the below two options:
1. Split with same dose;
2. Advance the dose earlier.

If options 1 and 2 fail consider increasing the dose but keeping it at/ below approved daily dose

If this strategy fails consider a complete switch of medication

OR

Complete switch to one of the options below

An α2δ calcium-channel ligand

OR

Rotigotine or a long-acting dopamine agonist at ≤ approved dose

If this strategy fails consider "**severe augmentation**" options

Severe augmentation

The objective is to reduce, and, if possible eliminate the short acting dopamine agonist and to begin treatment with rotigotine or a long acting dopamine agonist or an α2δ ligand
Two strategies are available for doing this:

Cross titration
Add an alpha-2-delta ligand and then gradually reduce the dose of the dopamine agonist with the objective of eliminating it altogether, understanding that this may not be possible

OR

Switch
Switch patient from a short-acting dopamine agonist to rotigotine or a long-acting dopamine agonist if this is not already the case.

OR

10-day washout

Evaluate if any drug treatment is needed.
If symptoms continue, introduce an α2δ ligand or an opioid

- If these strategies fail or if the patient has severe, round-the-clock symptoms, then treatment with low doses of an opioid (long-acting oxycodone or methadone) should be considered.
- If serum ferritin < 50-75 µg/mL then treatment with intravenous iron

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UNPROVEN APPROACHES TO REDUCE RLS

Clonazepam (Klonopin) or other benzodiazepines

Marijuana

TENS (transcutaneous electrical stimulation)

Relaxis (vibration)

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AUGMENTATION FROM HIGH DOSES OF ROPINIROLE, PART 1

53 yo man with 25-year history of RLS, initially occurring only at nocturnal awakenings. Brother, sister (mild) and mother have RLS.

Started on pergolide in 2000, with dose increase from 1 to 1.5 mg

Switched to ropinirole 1 mg in 2006, with 1) shortened duration of action requiring an additional nighttime dose, followed by 2) symptoms in early morning and then late afternoon, leading to 3) dose increase to 1 mg 4x/day, then over time to 2 mg 5x/day.

Gabapentin was added and ropinirole increased to 12 mg/day without benefit

Trials of adding Horizant and tramadol were not helpful

Ropinirole was increased to 4 mg 6x/day, with control of RLS symptoms

He had untreated sleep apnea, anemia without iron deficiency and was taking Paxil for an anxiety disorder. He had gained 25 lb/1 yr

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AUGMENTATION FROM HIGH DOSES OF ROPINIROLE, PART 2

Methadone 5 mg added at his first visit and increased to 10 mg over 2 months to 10 mg, while gradually reducing ropinirole to 3 mg, with improved though persistent RLS

Methadone dose was limited by some mild grogginess

Paxil, previously used for anxiety, was tapered off and gabapentin was added, leading to dizziness and nausea

Increased methadone to 15 mg/day, in divided doses to limit nausea

Gabapentin was increased to 600 mg twice per day (still combined with methadone and ropinirole 1.5 mg)

Ropinirole discontinued 7 months after first visit

Reintroduction of Paxil led to worsening of RLS

Increase in gabapentin to 900 mg three times/day allowed reduction of methadone to 7.5-10 mg/day

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Q & A

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