What is Augmentation?
How to diagnose?
What to do?

Diego Garcia-Borreguero

Madrid, SPAIN
Dopaminergics do work: The case of L-dopa

Benes et al, Sleep 1999.
But do dopaminergics work over the long-term?
Augmentation

- Augmentation reflects an overall increase in symptom severity as a result of long-term dopaminergic treatment.

- Augmentation does not have distinctive features to RLS itself, but rather represents a worsening of the same symptoms that are being treated.

- This worsening is usually slow and goes beyond baseline severity.
Augmentation

- First feature:
- Earlier onset of symptoms (main, cardinal feature)

(Allen et al., 1996)
Augmentation

- Shorter latency to symptoms at rest
- Overall increase in symptom severity
- Longer latency until onset of therapeutic effects
- Expansion to arms, trunk, abdomen

(Allen et al., 1996)
Dopaminergic Augmentation: No minor problem

Frequency in clinical practice

- Def. AUG 20%
- Partial AUG 56%
- No AUG 24%

Cumulative frequency

The risk to AUG increases during the first 8 years

(Allen, Sleep Med 2011)
Augmentation

Potential predictors:

- Dopaminergic treatment
- Short-acting drugs
- Dose
- Duration of treatment
- Lower ferritin at baseline
- Previous episodes of augmentation
- Previous loss of efficacy
Augmentation increases at higher doses

- 100 mg: 0%
- 200 mg: 14.3%
- 300 mg: 50%
- 400 mg: 28.6%
- 500 mg: 7.1%

Aver. dose: 329.81 ± 105 mg
Rate of Augmentation increases over time

Garcia-Borreguero et al., Mov Disord. 2012;27(2):277-83
Augmentation during treatment with Pramipexole vs Pregabalin

Augmentation at 40 weeks

Augmentation vs. disease progression

Augmentation occurs within weeks/months

Disease progression occurs slowly over time (years?)

Improvement of symptoms following dose reduction/ discontinuation of treatment becomes a key distinctive feature.
## Differences between tolerance and augmentation

<table>
<thead>
<tr>
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<th>Augmentation</th>
<th>Tolerance</th>
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<tbody>
<tr>
<td>Greater severity than at baseline</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Onset of symptoms earlier in the day</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Shorter latency to sx at rest</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Spread of sx to arms</td>
<td>Yes</td>
<td>No</td>
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Dose and augmentation/ tolerance

- Higher doses of dopaminergic treatment result in a higher incidence of augmentation

- Lower doses of dopaminergic treatment result in a higher incidence of tolerance
Severity

Untreated

Treated

Tolerance

AUGMENTATION

MPI criteria

clinically significant Sx

Time
Early signals of Augmentation

- Break-through crises/ daytime symptoms
- Increase in symptom frequency or symptom intensity
- Overall decrease in therapeutic efficacy/ tolerance
- Shorter duration of treatment effect.
- Symptoms in previously unaffected body parts
- Worsening of sleep efficacy or sleep quality
- Increased PLMs during sleep or wakefulness
- Patient requires additional medication
What causes augmentation?

- **Pharmacokinetic hypothesis**
  - Based on difference in prevalences during treatments with DA agonists (low prev.) and L-DOPA (high prevalence)
  - Caused by repeated (=“pulsatile”) administration?

- **Downregulation of DA receptors** during long-term L-DOPA treatment
  - Related to pulsatile administration of L-DOPA?
  - Related to dose, duration of treatment?
Diagnosis of Augmentation

- Relies on clinical judgement (MPI criteria)
- Structured Interview for the Diagnosis of Augmentation (based on Max-Planck criteria)
- Clinical trials: Expert Pannel on Augmentation

- Potential alternatives:
  - Actigraphy
  - Multiple Suggested Immobilization test
  - BUT: None of these has been used yet in clinical studies.

- Evaluation of Severity: Augmentation Severity Rating Scale: ASRS
Prevention of augmentation

1. Keep ferritin levels within the normal range
2. Avoid SSRIs, antihistamines
3. Use long-acting dopamine agonists
4. Keep the dose low, try to stay well below the upper limit of the recommended dose range.
5. If some, but insufficient efficacy, consider combination treatment with a non-dopaminergic agent (i.e. alpha2-delta ligand)
Proposed Management of Augmentation

- First, determine ferritin levels and evaluate potential yatrogenic factors (SSRI, DA antagonists!)

- Mild cases: Anticipate the time of administration of DA drugs.

- Severe cases:
  - **Option A**: Progressive withdrawal of dopaminergic drug. Combination therapy with alpha-2 delta ligands /opiates
  - **Option B**: Complete interruption of DA drugs. Administration of alpha-2 delta ligands /opiates
  - Continue options A or B for 3-6 months. Then reinitiate treatment with a different dopaminergic agent.
  - If augmentation reappears, continue monotherapy with opiates/alpha-2 delta ligands either as monotherapy or in combination with low doses of dopaminergic drugs.