RLS WEBINAR SERIES 2017

RESTLESS LEGS SYNDROME FOUNDATION

The Prevention & Treatment of Augmentation

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What is Augmentation?

A worsening of RLS after an initial improvement with a dopamine medication

- Levodopa (Sinemet)
- Pramipexole (Mirapex)
- Ropinirole (Requip)
- Rotigotine (Neupro patch)
- Cabergoline (Dostinex)

What is Augmentation?

A worsening of RLS after an initial improvement with a dopamine medication

Also occurs with tramadol (Ultram)

- Pain pill related to opioids

When was Augmentation first described?

Richard Allen – 1996

- “Augmentation of the restless legs syndrome with carbidopa/levodopa.”
- Occurred in 82% of RLS patients
- Worse with higher doses
- Resolved by stopping or decreasing the medication

Augmentation – NIH Criteria

Worsening RLS symptoms after starting DA therapy (usually months to years)

- Earlier onset by at least 2 hours
- Increase in intensity of symptoms
- Quicker onset of symptoms with rest
- Medication effect does not last as long
- Spread of symptoms to other body parts
- PLMW occur for the first time or are worse

Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. Sleep Med 2003;4:101–19.

Simplified Version

Consider that augmentation may be present whenever a patient who has been on stable treatment for at least 6 months requests more medication.

Rule out:

- Triggers
- Low iron
- Natural worsening

Garcia-Borreguero D1, Silber MH2, Winkelman JW3, Högl B4, Bainbridge J5, Buchfuhrer M6, Hadjigeorgiou G7, Inoue Y8, Manconi M9, Oertel W10, Ondo W11, Winkelmann J12, Allen RP13. Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. Sleep Med. 2016 May;21:1-11.

Rule out other similar conditions

Table 2
Differential diagnosis of augmentation.

	Augmentation	End of dose rebound	Tolerance	Natural progression	Exacerbating factors*
Worse than before treatment	Yes	Yes, in early morning	No	Yes	Yes
Earlier onset	Yes	Yes, in early morning	No	Yes	Yes
Spread to arms	Yes	No	No	Yes	Yes
Breakthrough at night	Yes	Yes, in early morning	Yes	Yes	Yes
Worse with increased dose	Yes, but not immediately	No	No	No	No
Improved with decreased dose	Yes, but not always†	No	No	No	No

* For example, low serum ferritin, medications, increased immobility.
† Eventually augmentation is overcome when the dose is decreased; and while augmentation symptoms can improve within 72 h on levodopa, it can take several weeks to several months to see an improvement with dopamine agonists.

Garcia-Borreguero D1, Silber MH2, Winkelman JW3, Högl B4, Bainbridge J5, Buchfuhrer M6, Hadjigeorgiou G7, Inoue Y8, Manconi M9, Oertel W10, Ondo W11, Winkelmann J12, Allen RP13. Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. Sleep Med. 2016 May;21:1-11.

What is causing Augmentation?

Downregulation of the dopamine receptor?

- Similar to tolerance

Imbalance of Dopamine Receptor Subtypes

- D1, D2, D3, D4, D5

Early signs of changes in RLS with DA

How common is Augmentation?

Levodopa – 82%

Mirapex – 7-8%/year

Neupro – 5% after 5 years with 1-3 mg
- Less common with longer-acting DA?

Over 75% of referrals to national RLS experts

Recommended Dopamine Drug Doses

Table 6
Suggested initial dose and maximum recommended dose for dopamine agonists.

	Initial dose	Max. recommended dose
Pramipexole	0.125 mg/day	0.75 mg/day
Ropinirole	0.25 mg/day	4 mg/day
Rotigotine	1 mg/day	3 mg/day

Garcia-Borreguero D1, Silber MH2, Winkelman JW3, Högl B4, Bainbridge J5, Buchfuhrer M6, Hadjigeorgiou G7, Inoue Y8, Manconi M9, Oertel W10, Ondo W11, Winkelmann J12, Allen RP13. Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. Sleep Med. 2016 May;21:1-11.

How do most doctors & specialists treat Augmentation?

Typically, they increase the dose of the dopamine drug which provides temporary improvement

- Mirapex up to 8 mg
- Ropinirole up to 24-48 mg
- Neupro up to 8-16 mg (often combined with other DA)
- Add gabapentin (alpha-2-delta) type drugs

Task Force Article

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Original Article

Guidelines for the first-line treatment of restless legs syndrome/ Willis–Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation

Diego Garcia-Borreguero [a,*], Michael H. Silber [b], John W. Winkelman [c,d], Birgit Högl [e], Jacquelyn Bainbridge [f], Mark Buchfuhrer [g,h], Georgios Hadjigeorgiou [i], Yuichi Inoue [j,k], Mauro Manconi [l], Wolfgang Oertel [m], William Ondo [n], Juliane Winkelmann [o,p,q], Richard P. Allen [r,s]

Garcia-Borreguero D1, Silber MH2, Winkelman JW3, Högl B4, Bainbridge J5, Buchfuhrer M6, Hadjigeorgiou G7, Inoue Y8, Manconi M9, Oertel W10, Ondo W11, Winkelmann J12, Allen RP13. Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. Sleep Med. 2016 May;21:1-11.

Prevention of Augmentation

Do not use dopamine drugs

Choose an alpha-2-delta drug as first line therapy unless contraindicated, side effects occur or they are not effective

Garcia-Borreguero D1, Silber MH2, Winkelman JW3, Högl B4, Bainbridge J5, Buchfuhrer M6, Hadjigeorgiou G7, Inoue Y8, Manconi M9, Oertel W10, Ondo W11, Winkelmann J12, Allen RP13. Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. Sleep Med. 2016 May;21:1-11.

Prevention of Augmentation

When using dopamine drugs

- Use the lowest possible dose (but may occur with the lowest dose)
- Consider intermittent use (up to 3/week)
- Do not increase the dose more than once
- Do not change to another short-acting DA
- Consider using longer acting DA – Neupro

Keep ferritin levels as high as possible

Garcia-Borreguero D1, Silber MH2, Winkelman JW3, Högl B4, Bainbridge J5, Buchfuhrer M6, Hadjigeorgiou G7, Inoue Y8, Manconi M9, Oertel W10, Ondo W11, Winkelmann J12, Allen RP13. Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. Sleep Med. 2016 May;21:1-11.

Approved Dopamine Drug Doses

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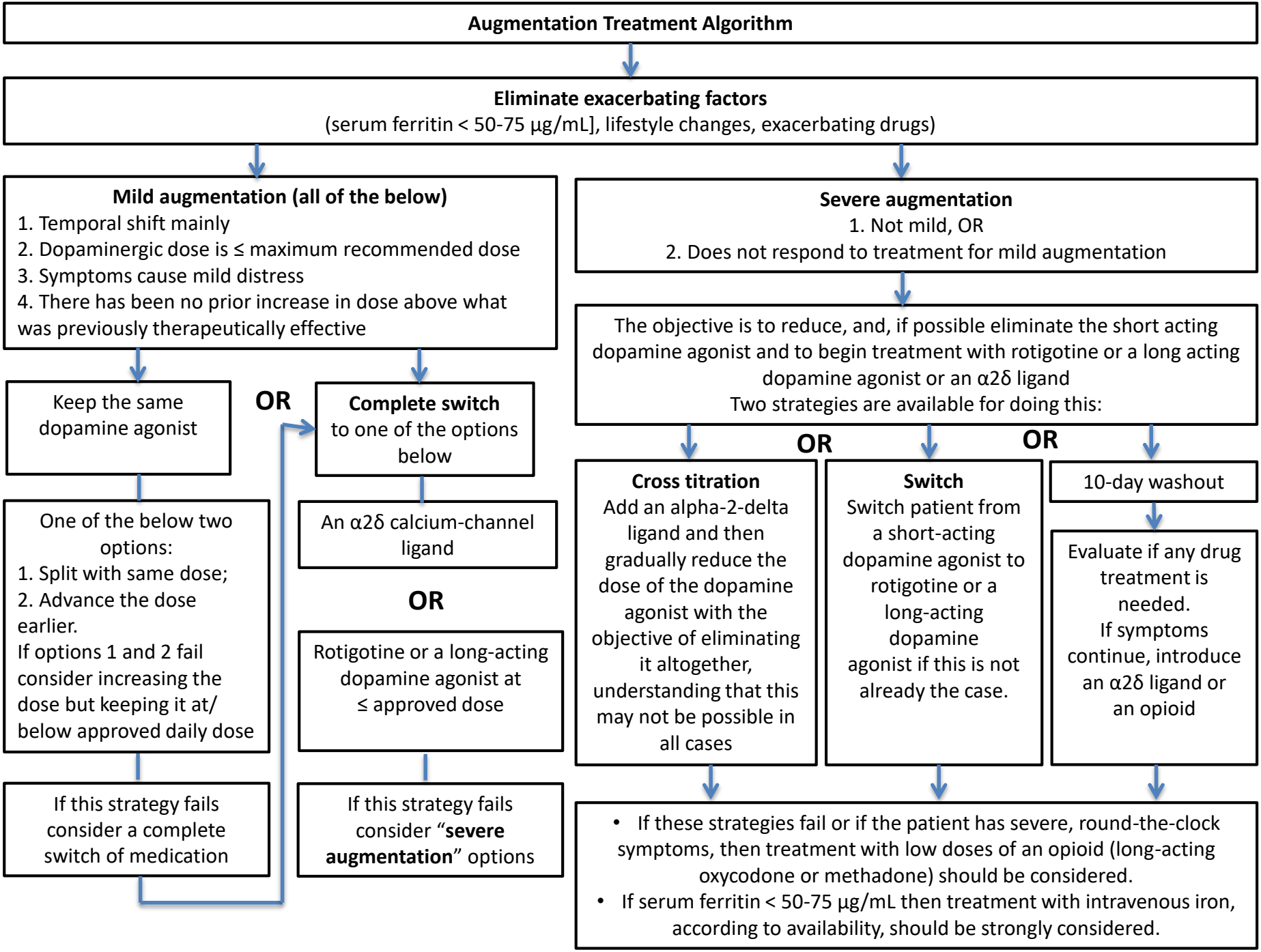
Dr. Buchfuhrer's Maximum Dopamine Drug Doses

Pramipexole (Mirapex)	.25 mg
Ropinirole (Requip)	1 mg
Rotigotine (Neupro)	3 mg



Garcia-Borreguero D. et al. Available at: http://irlssg.org/wp-content/uploads/2015/05/Summary-of-recommendations-RLS-Augmentation-May-2015.pdf

Augmentation Treatment Algorithm

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

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Augmentation Treatment Algorithm

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

Mild augmentation (all of the below)
1. Temporal shift mainly
2. Dopaminergic dose is ≤ maximum recommended dose
3. Symptoms cause mild distress
4. There has been no prior increase in dose above what was previously therapeutically effective

Severe augmentation
1. Not mild, OR
2. Does not respond to treatment for mild augmentation

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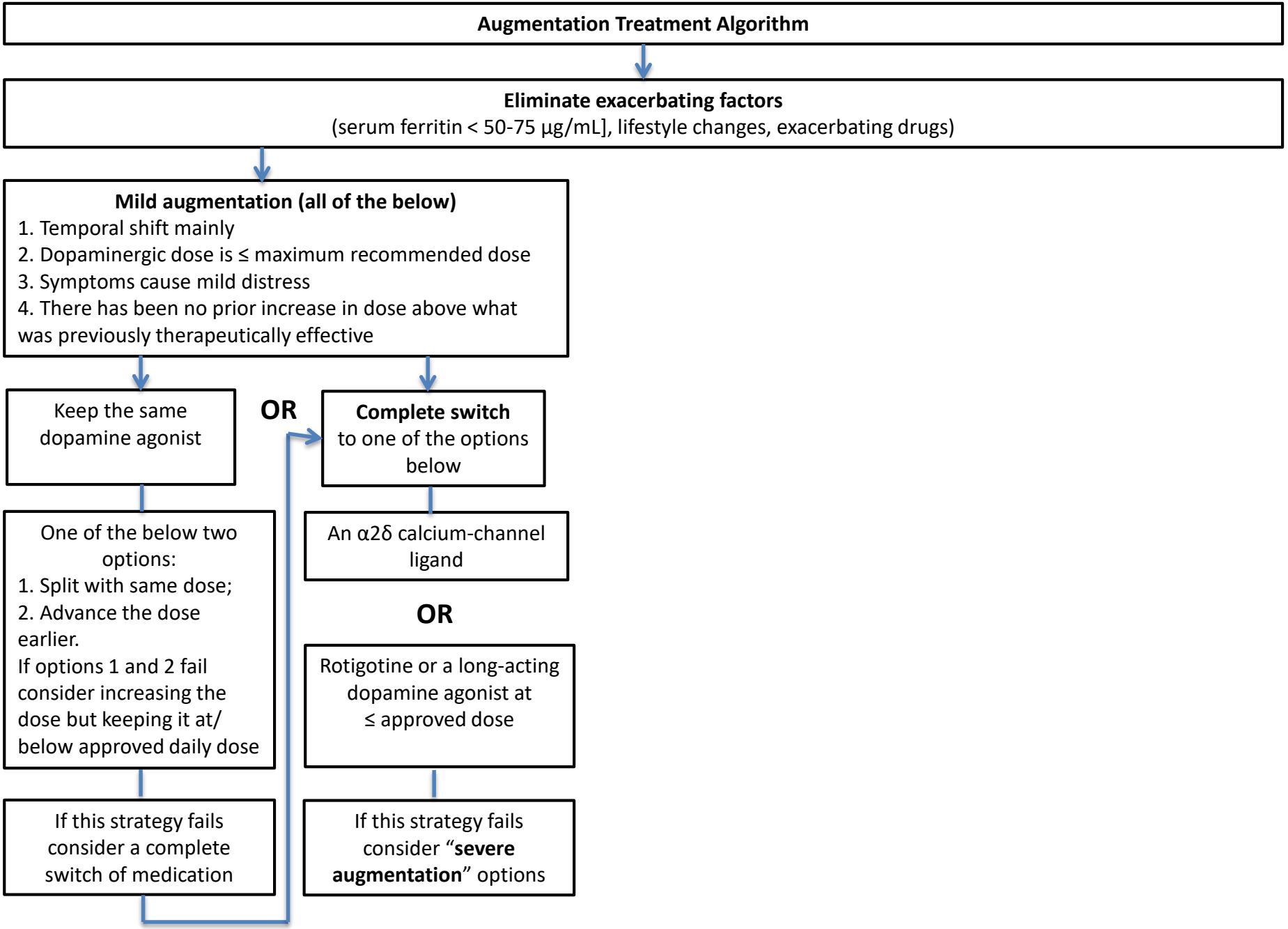

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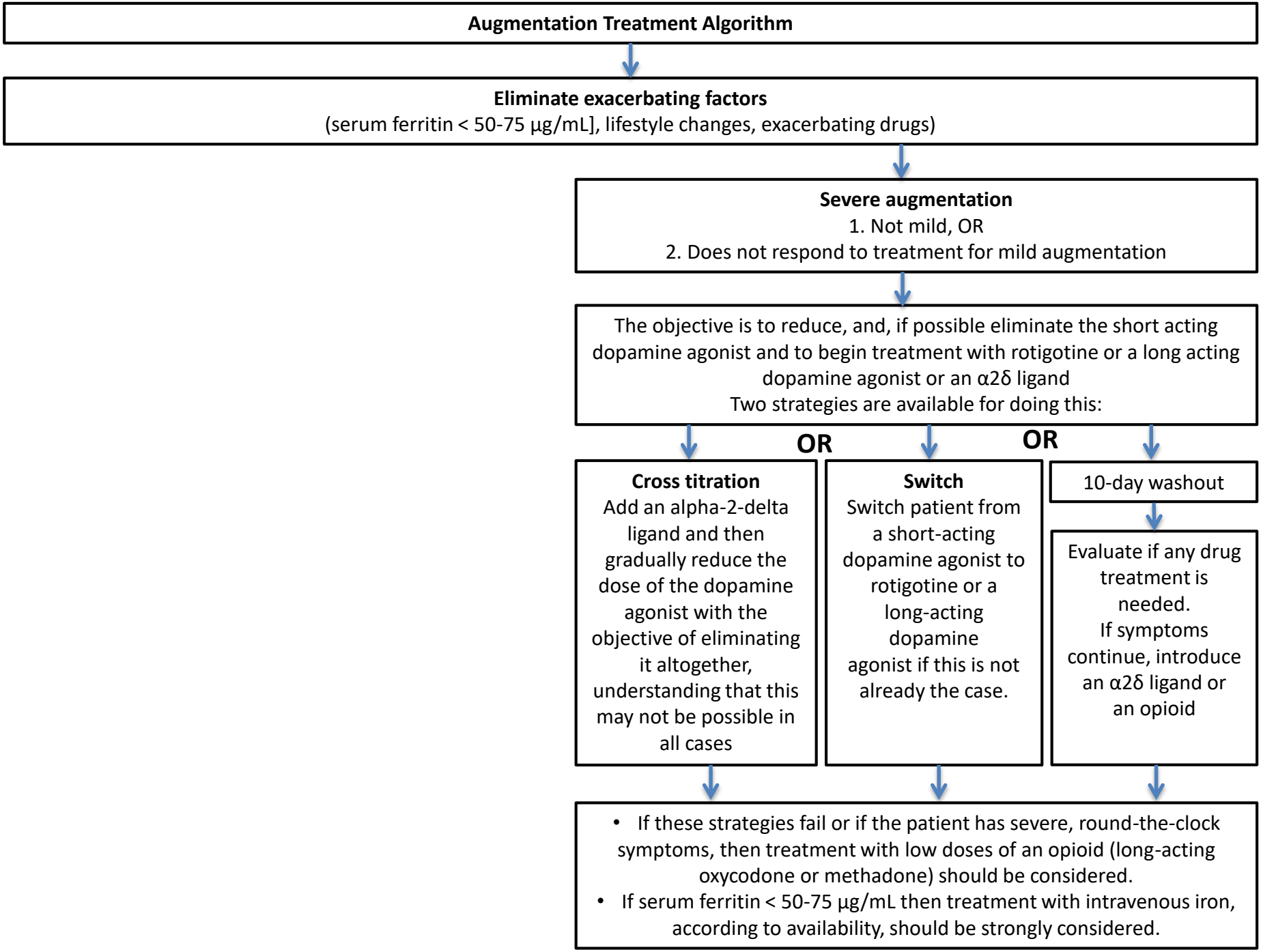

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Question & Answer

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