Guidelines for the first-line treatment of RLS 2016

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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 D, Silber MH, Winkelman JW et al. 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.

Recommendation for initial treatment

- A treatment trial with α2δ ligands may be considered for initial treatment

Augmentation

- First described by Allen & Earley in 1996
  - 82% of patients on carbidopa/levodopa
  - Resolved with cessation of medication
  - Dose related

Allen RP, Earley CJ. Augmentation of the restless legs syndrome with carbidopa/levodopa. Sleep 1996;19:205–13.

Augmentation – NIH Criteria

- Worsening RLS symptoms after starting levodopa, a Dopamine Agonist (DA) or tramadol
  - usually months to years
- Earlier onset by at least 2 hours
- Increase in intensity of symptoms

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.

Augmentation – NIH Criteria

- 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.

Max Planck Institute Criteria

A: Basic features (all of which need to be met):

1) The increase in symptom severity was experienced on five out of seven days during the previous week;
2) The increase in symptom severity is not accounted for by other factors such as a change in medical status, lifestyle or the natural progression of the disorder;
3) It is assumed that there has been a prior positive response to treatment.

In addition, either B or C or both have to be met:

B. Persisting (although not immediate) paradoxical response to treatment: RLS symptom severity increases some time after a dose increase, and improves some time after a dose decrease.

C. Earlier onset of symptoms:

1) An earlier onset by at least four hours.

OR

2) An earlier onset (between two and four hours) occurs with one of the following compared to symptom status before treatment:
   a) Shorter latency to symptoms when at rest;
   b) Spreading of symptoms to other body parts;
   c) Intensity of symptoms is greater (or increase in periodic limb movements [PLM] if measured by polysomnography [PSG] or the suggested immobilization test [SIT]);
   d) Duration of relief from treatment is shorter.

Augmentation requires criteria A + B or A + C or A + B + C to be met.

Garcia-Borreguero D, Allen RP, Kohnen R, Hogl B. Diagnostic standards for dopaminergic augmentation of restless legs syndrome: report from a World Association of Sleep Medicine –IRLSSG consensus conference at the Max Planck Institute. Sleep Med 2007;8:520–30.

Augmentation Severity Rating Scale

Item 1 During the past week, at what time did your RLS symptoms usually start?

Please write down the time when the symptoms usually started (e.g.: 22:45). |_|_|:|_|_| (HH MM) 24-hr clock

Item 2 During the past week, at any times you were sitting or resting (for example in a car, plane, theatre or watching TV) how soon afterwards did your RLS symptoms usually start?

Please indicate the time it takes for symptoms to start at various times during the day (late morning, early afternoon, late afternoon, evening before taking any RLS medication).

2a When sitting in the late morning (i.e., before noon), your symptoms usually started…

2b When sitting in the early afternoon (i.e., 12:00 – 15:00), your symptoms usually started…

2c When sitting in the late afternoon (i.e., 15:00 – 18:00), your symptoms usually started…

2d When sitting in the evening (after 18:00, before taking the first dose of RLS medication), your symptoms usually started…

2a	2b	2c	2d		
☐	☐	☐	☐	0 =	After a very long time or never
☐	☐	☐	☐	1 =	After a long time (i.e., after about an hour)
☐	☐	☐	☐	2 =	After a moderate amount of time (i.e., after about half an hour)
☐	☐	☐	☐	3 =	After a short time (i.e., within a few minutes)
☐	☐	☐	☐	4 =	Immediately or almost immediately
☐	☐	☐	☐	-9 =	Did not sit or rest over the last week

Item 3 During the past week, what parts of your body are usually affected by RLS symptoms?

García-Borreguero et. al. Validation of the Augmentation Severity Rating Scale (ASRS): a multicentric, prospective study with levodopa on restless legs syndrome. Sleep Med. 2007 Aug;8(5):455-63

Consider Augmentation

- Whenever a patient who has been on stable treatment for at least 6 months requests more medication

- Other conditions to rule out:
  - Exacerbating medications
  - Low iron levels
  - Comorbid conditions
  - Change in lifestyle
  - Increased stress/anxiety/depression

Augmentation or Natural Worsening of RLS?

- Can be very similar
- Augmentation gets worse with an increase in DA dose
  - May take months to years
  - Look back at the previous dose increases
- Augmentation gets better with a decrease in DA dose
  - Within a few days with levodopa
  - Usually 10-14 days with dopamine agonists
    - But can be several weeks to months
    - RLS symptoms are extremely severe

What Causes Augmentation?

DA	Receptor type affinities
Pramipexole	High, with $D_3 > D_4 > D_2 >> D_{1,5}$
Ropinirole	Very high, with $D_3 >> D_{2,4} >> D_{1,5}$
Rotigotine	High, with $D_3 > D_2 >> D_1$

Clemens S, Rye D, Hochman S. Restless legs syndrome: revisiting the dopamine hypothesis from the spinal cord perspective. Neurology. 2006;67(1):125-130.

What Causes Augmentation?

Exploratory cross-over, trial of augmented RLS with the dopamine receptor 1/5 antagonist ecopipam D1/D5 antagonist ecopipam for augmented RLS

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ABSTRACT

Background: Restless legs syndrome (RLS) is a common condition that initially responds dramatically to dopaminergic therapy. Over time, however, dopaminergics cause augmentation, where symptoms occur earlier and intensify. Animal models suggest this may result from increased dopamine receptor type-1 affinity in the spinal cord. Ecopipam is a potent, specific dopamine-1/5 receptor antagonist.

Methods: We performed a small ($N = 10$) exploratory placebo controlled, cross-over safety trial of ecopipam (25–100 mg/day) for patients with augmented RLS currently taking dopamine agonists.

Results: Ecopipam was well tolerated with sedation being the most common adverse event in drug and placebo. Safety scales and serology data were similar to placebo. The study was not powered to demonstrate efficacy and exploratory efficacy data showed no significant improvement compared to placebo, but RLS diaries, the international RLS rating scale, and clinical global impressions all favored drug. No subject worsened on drug or demonstrated rebound worsening after drug discontinuation.

Conclusion: Ecopipam was safe and well tolerated in this initial study for RLS. Given the lack of alternate options, larger efficacy studies for augmented RLS, and potentially de novo RLS are justified.

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KEYWORDS
Ecopipam; D1 antagonist; restless legs syndrome; augmentation; clinical trial

William G Ondo, Titilayo Olubajo. Exploratory cross-over, trial of augmented RLS with the dopamine receptor 1/5 antagonist ecopipam D1/D5 antagonist ecopipam for augmented RLS. INTERNATIONAL JOURNAL OF NEUROSCIENCE 2022, VOL. 132, NO. 8, 778–782

How Common is Augmentation?

- Rate of 7-8% per year with pramipexole
- 75% of cases referred to RLS experts

Silver N, Allen RP, Senerth J, Earley CJ. A 10-year, longitudinal assessment of dopamine agonists and methadone in the treatment of restless legs syndrome. Sleep Med. 2011 May;12(5):440-4.
Allen RP, Ondo WG, Ball E, et al. Restless legs syndrome (RLS) augmentation associated with dopamine agonist and levodopa usage in a community sample. Sleep Med 2011;12:431–9.
Allen RP, Chen C, Garcia-Borreguero D, et al. Comparison of pregabalin with pramipexole for restless legs syndrome. N Engl J Med 2014;370:621–31.

Preventing Augmentation

- Treat initially with a non-dopamine drug
  - Consider the risks and benefits of treatments
  - Cost and availability

- Do not change from one short acting dopamine agonist to another

Augmentation Treatment

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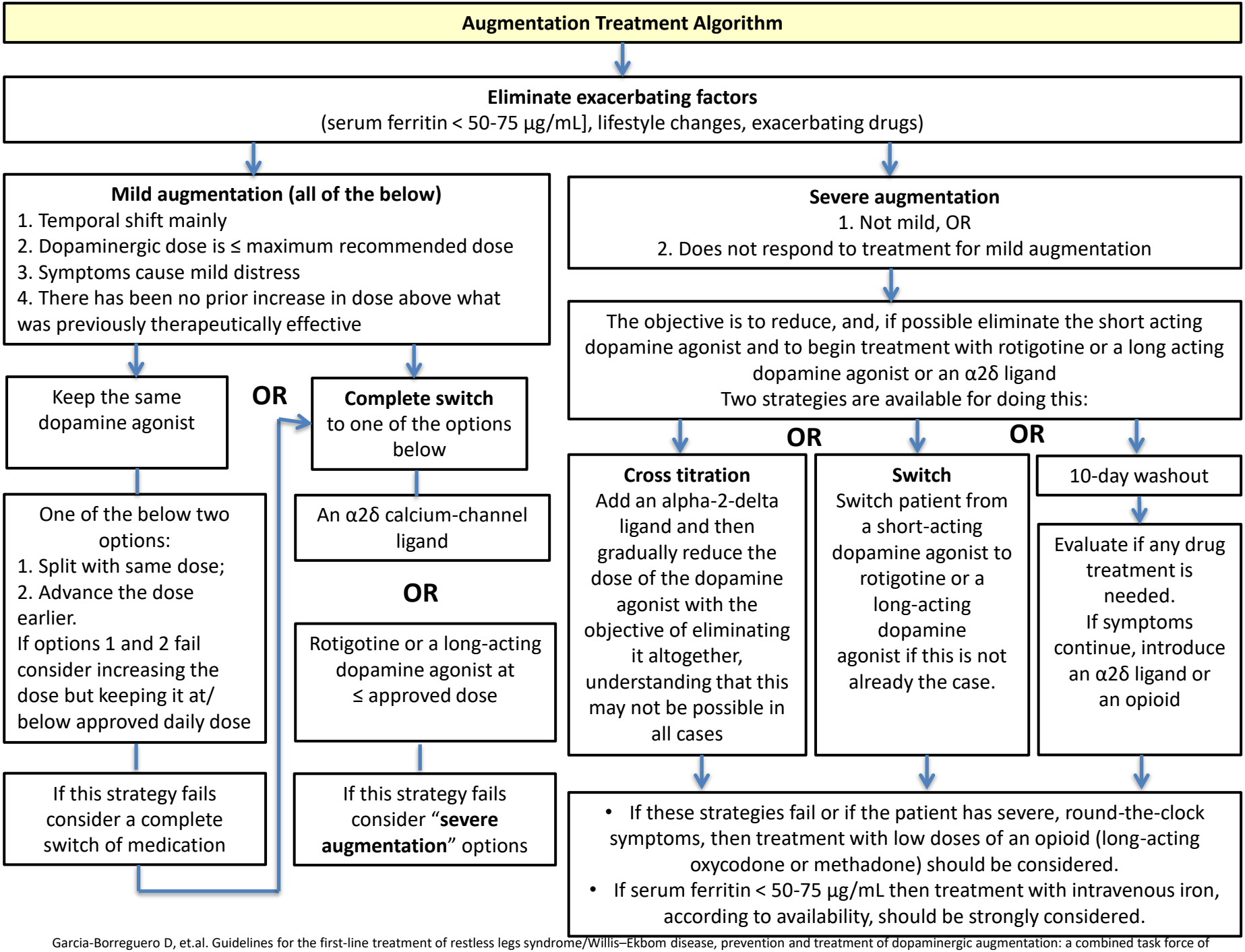

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Augmentation Treatment Algorithm

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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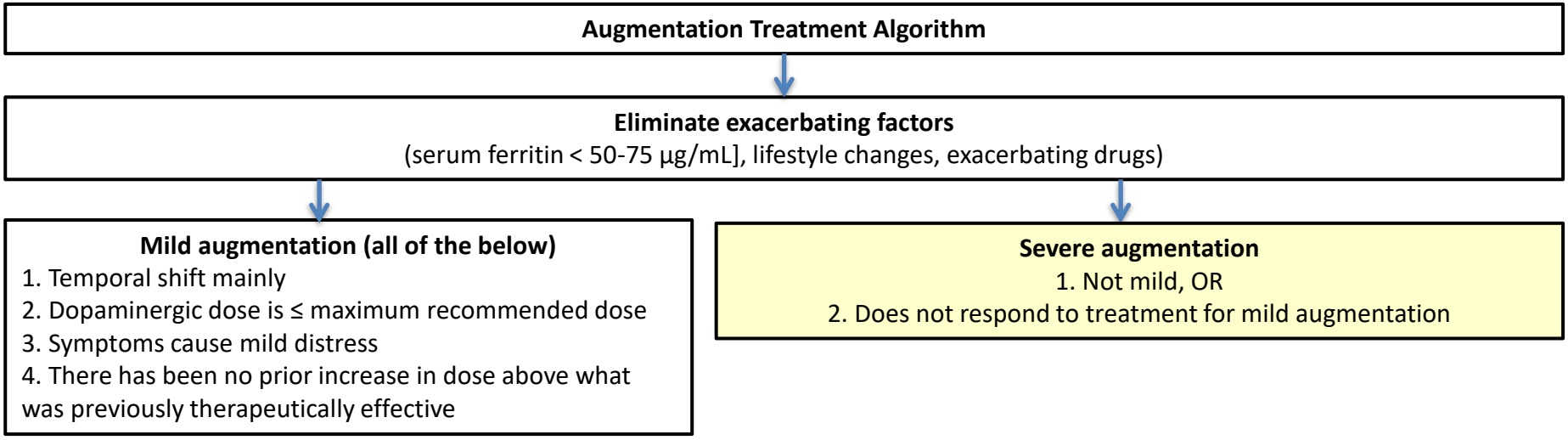

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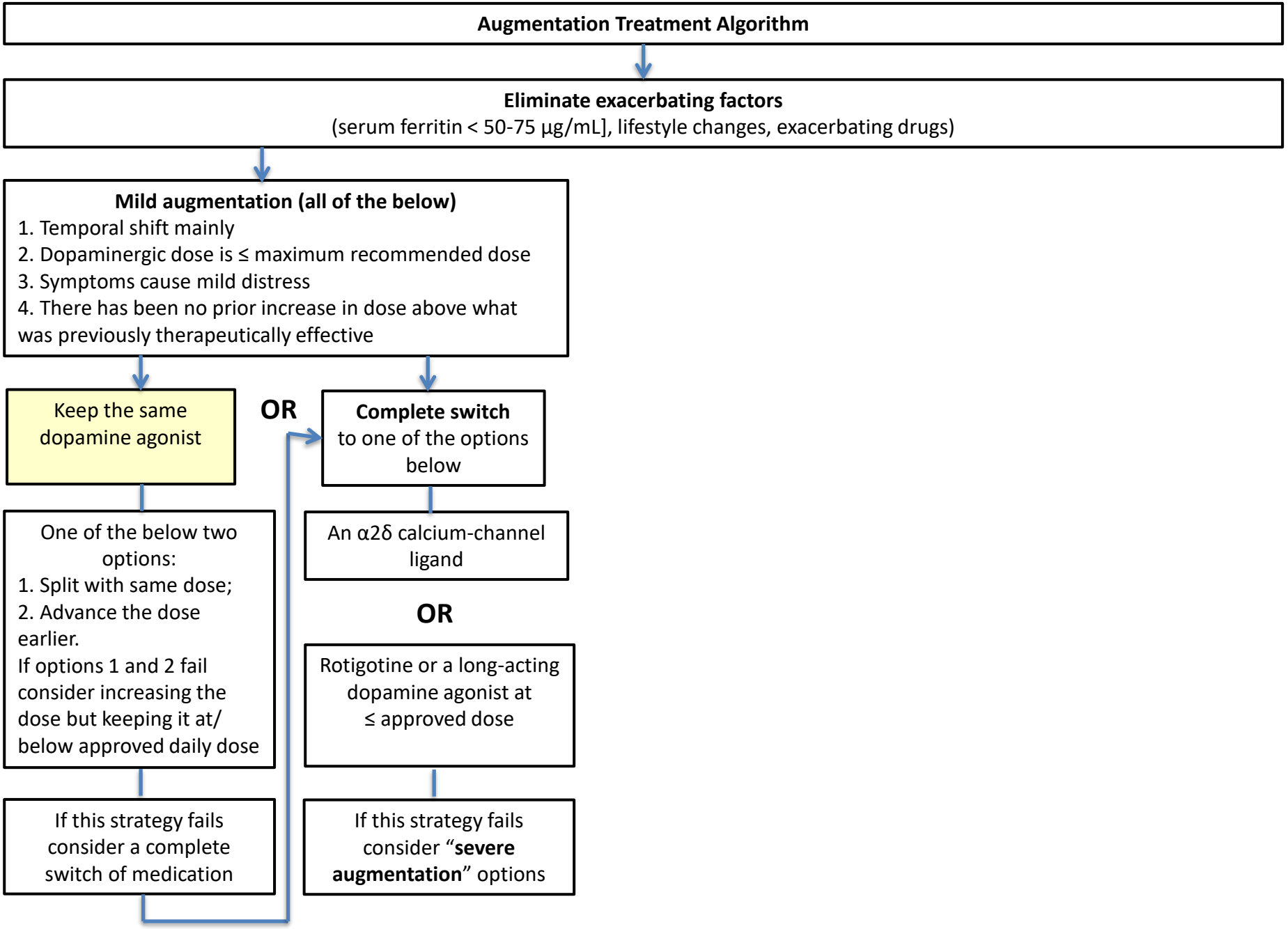

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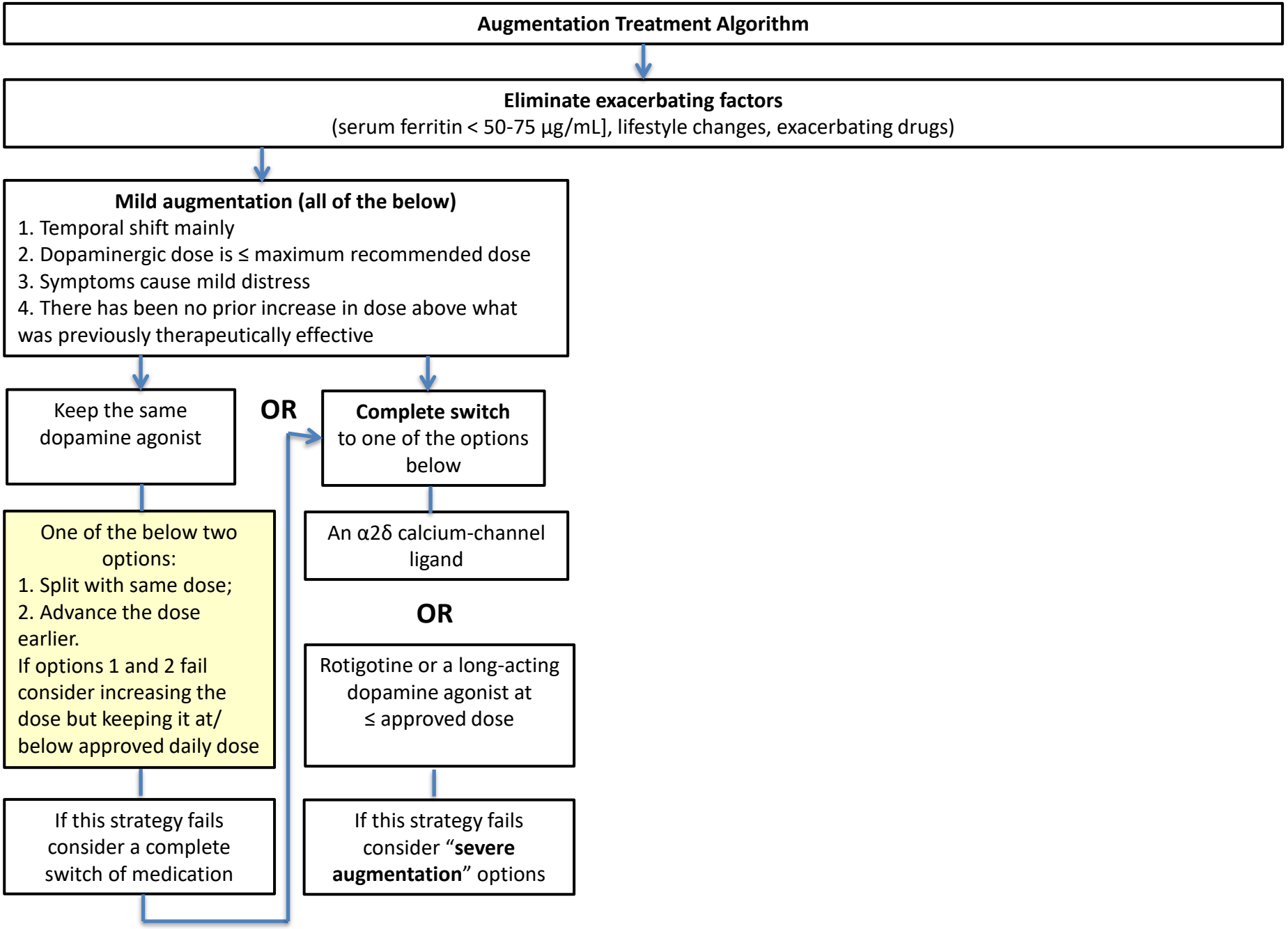

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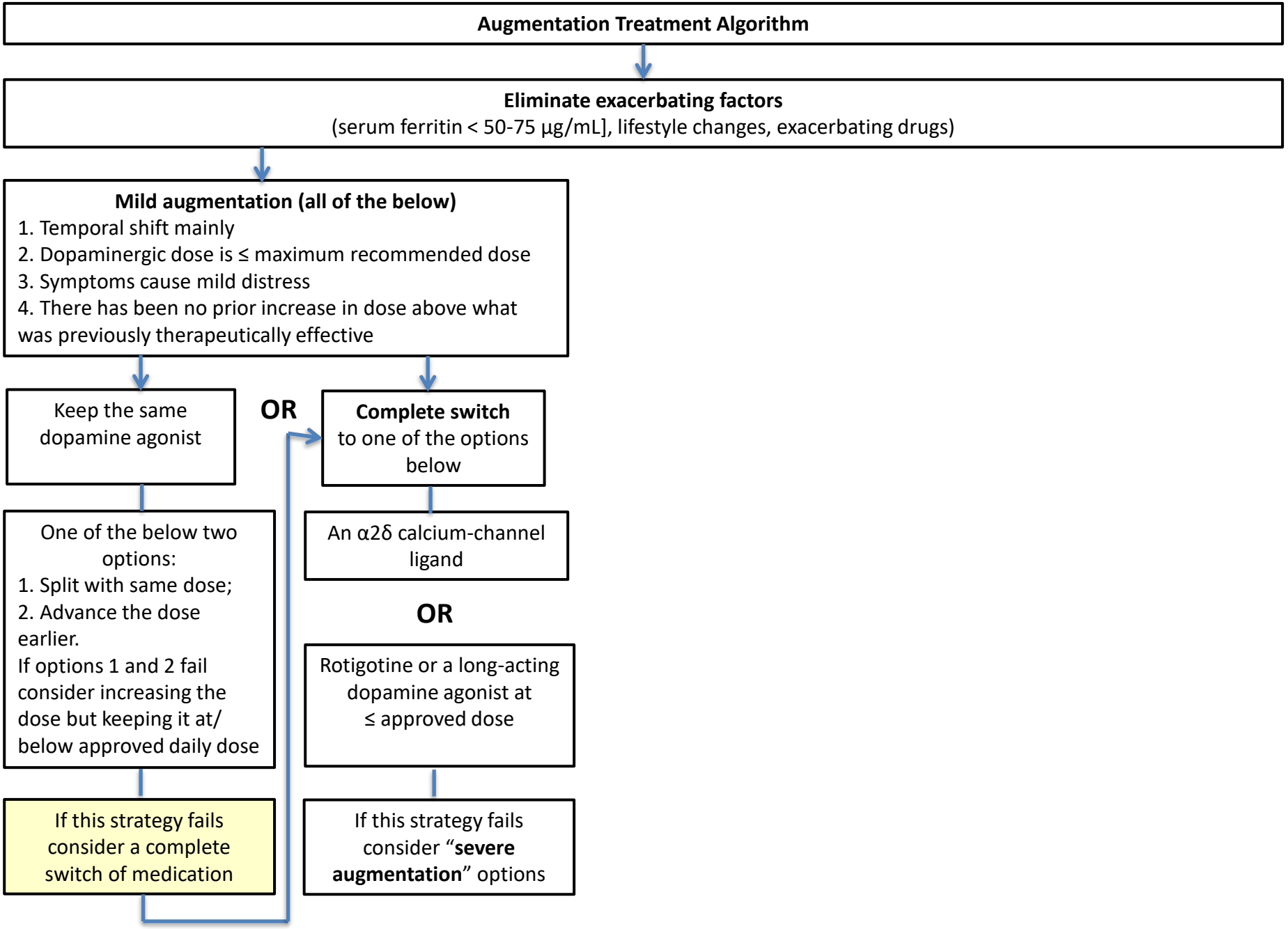

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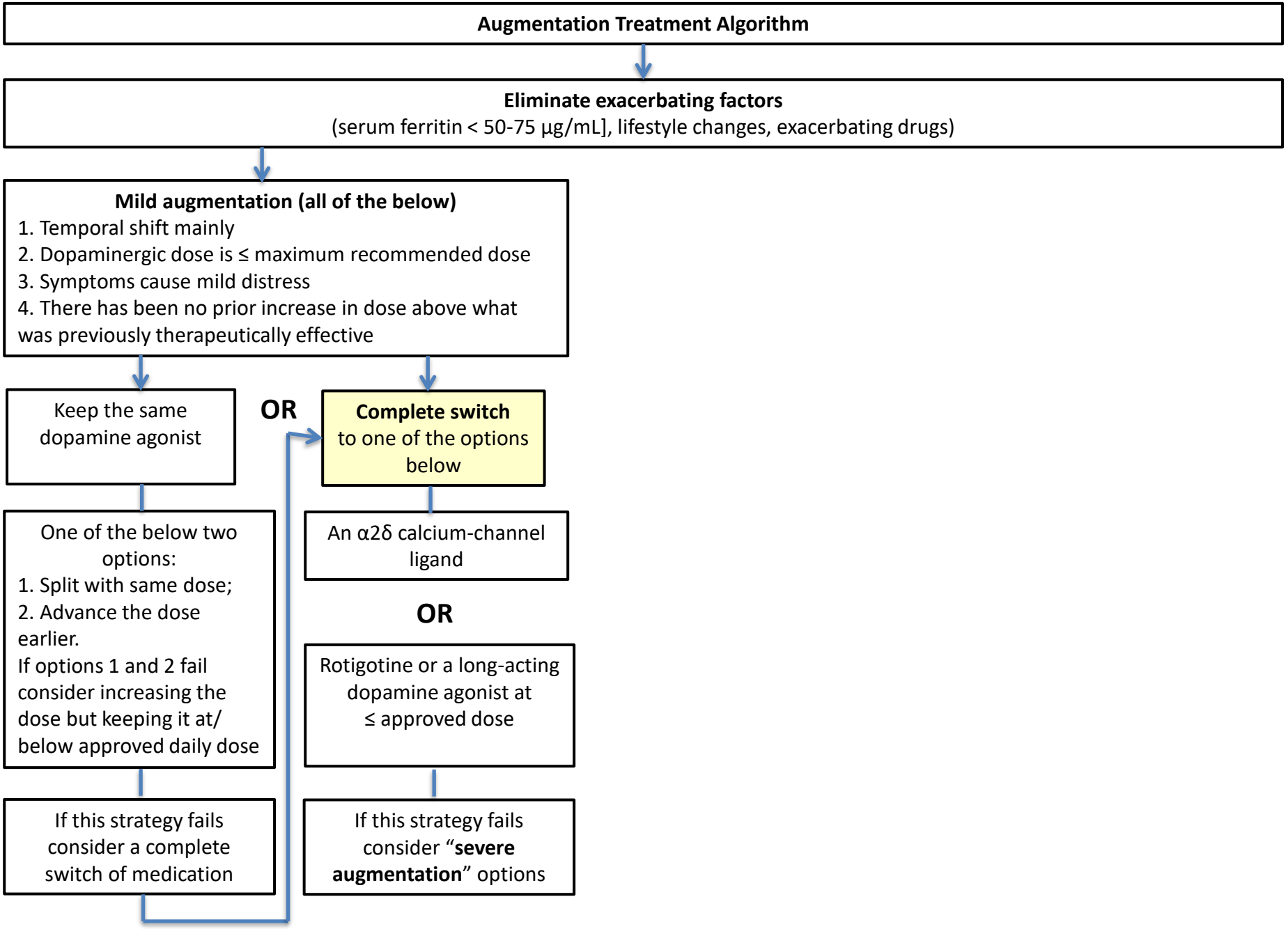

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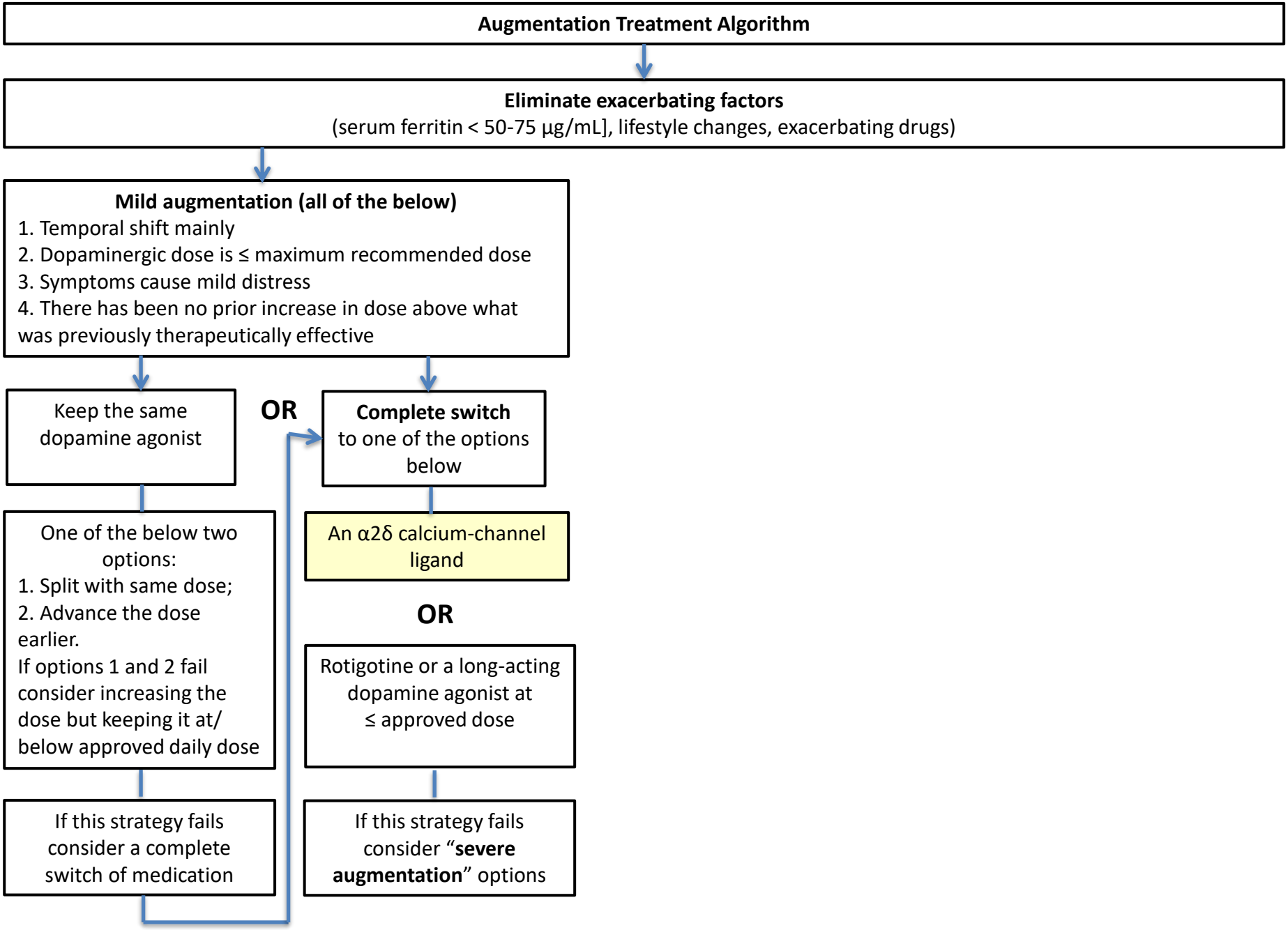

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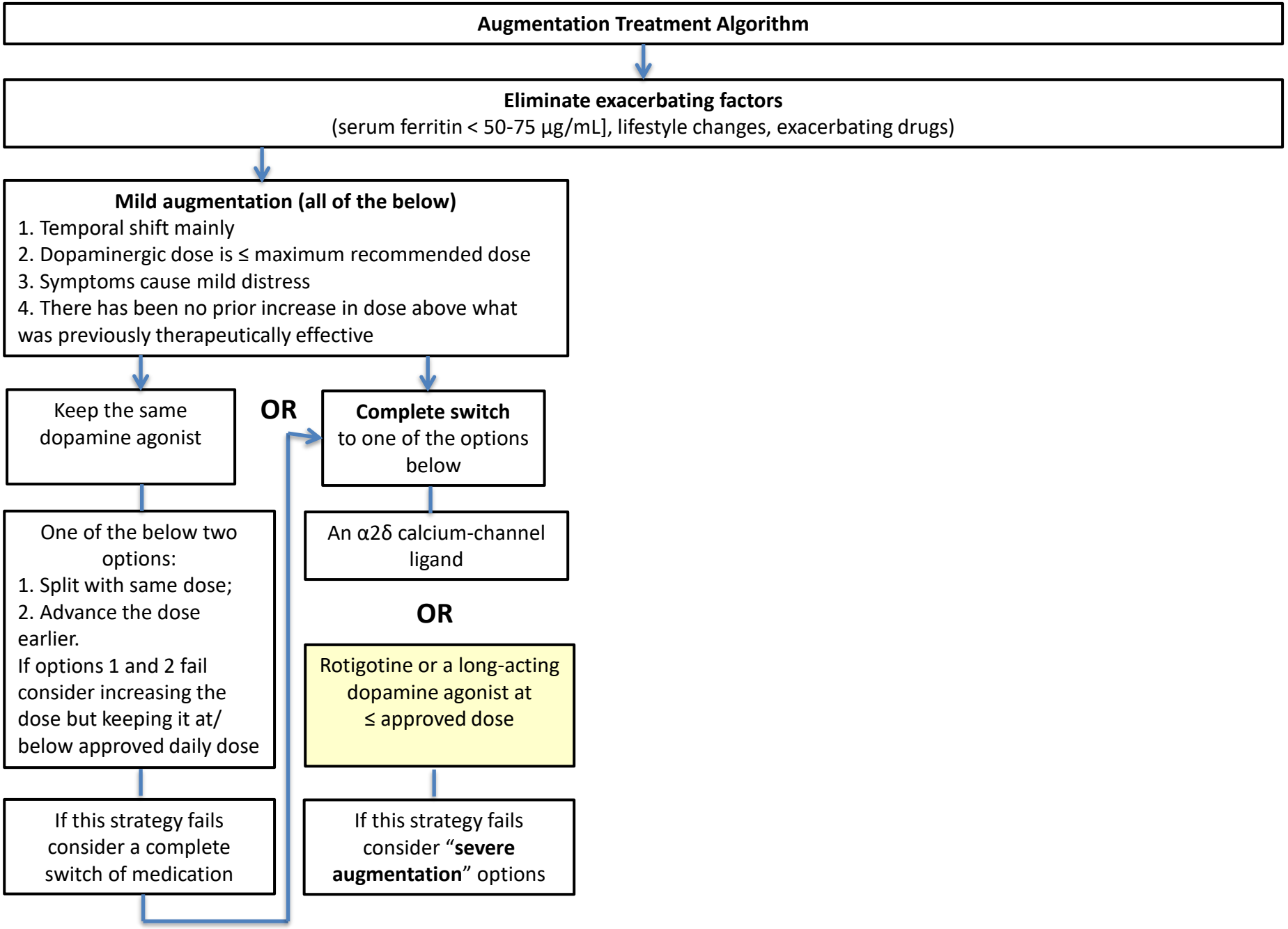

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Switching to a Long Acting DA Initial Dose

	Rotigotine (Approved)	Pramipexole ER (Not Approved)
Pramipexole		
.25 mg	2 mg	.375 mg
.50 mg or higher	3 mg	.75 mg
Ropinirole		
.5-1.0 mg	2 mg	.375 mg
2 mg or higher	3 mg	.75 mg

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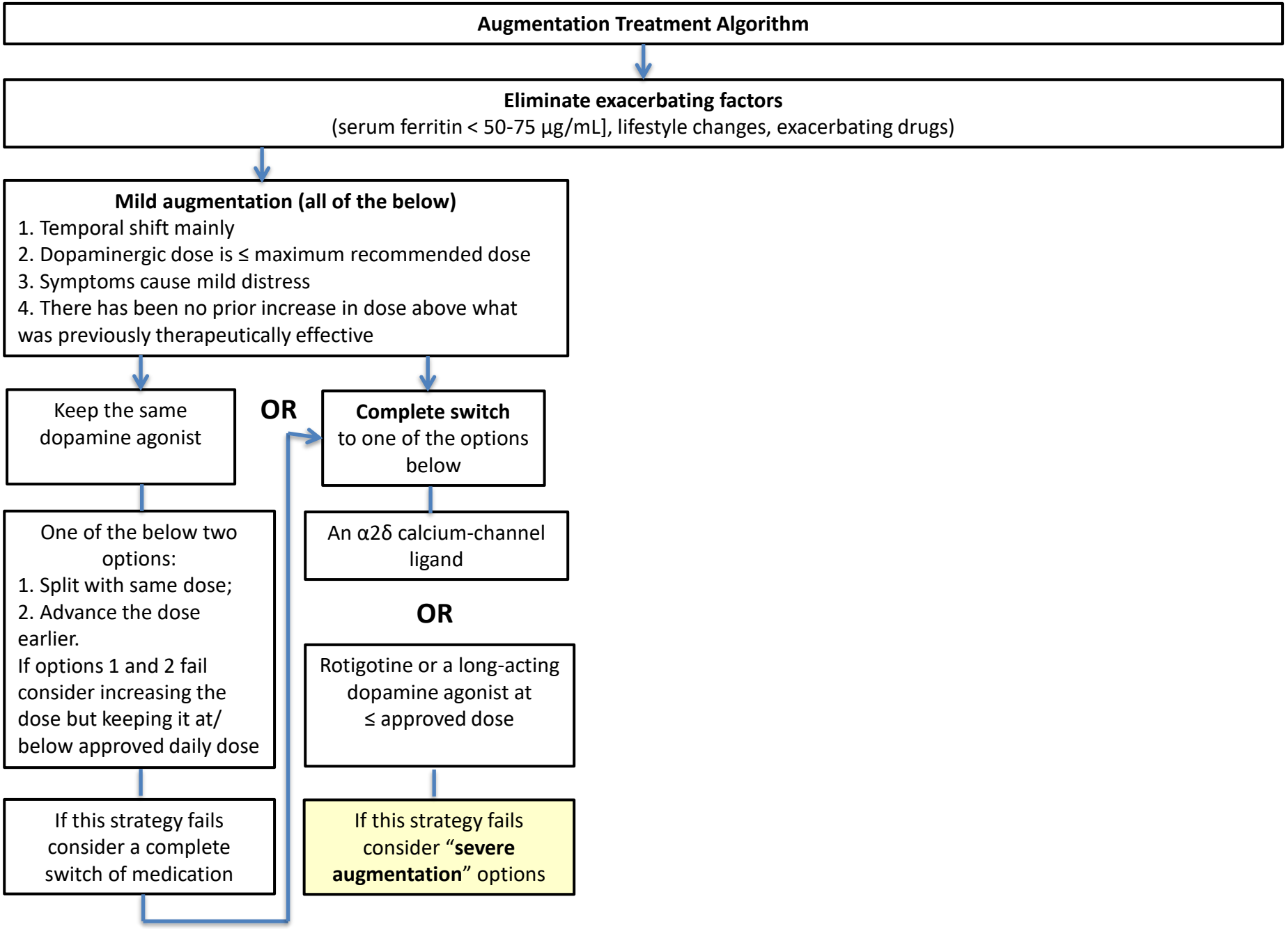

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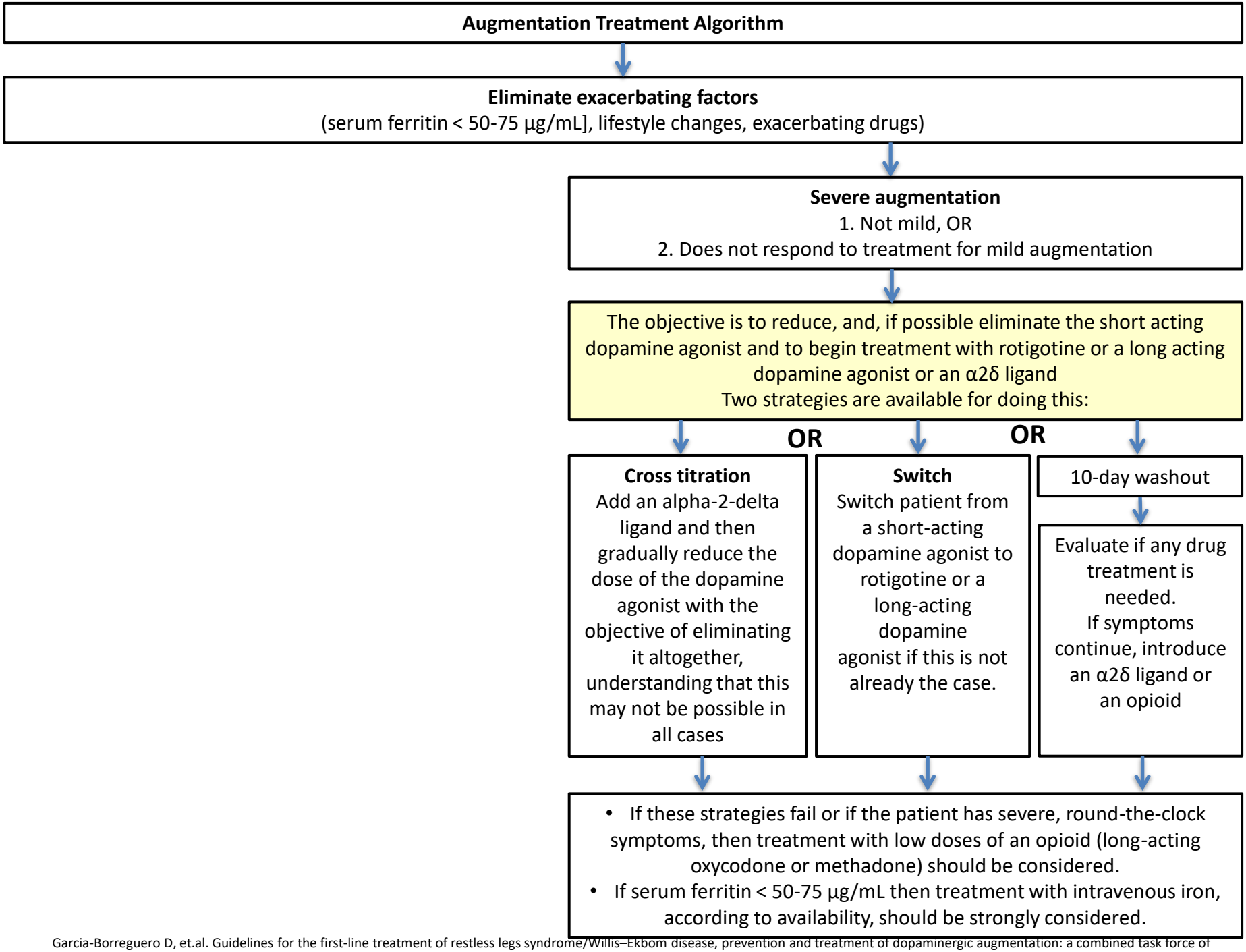

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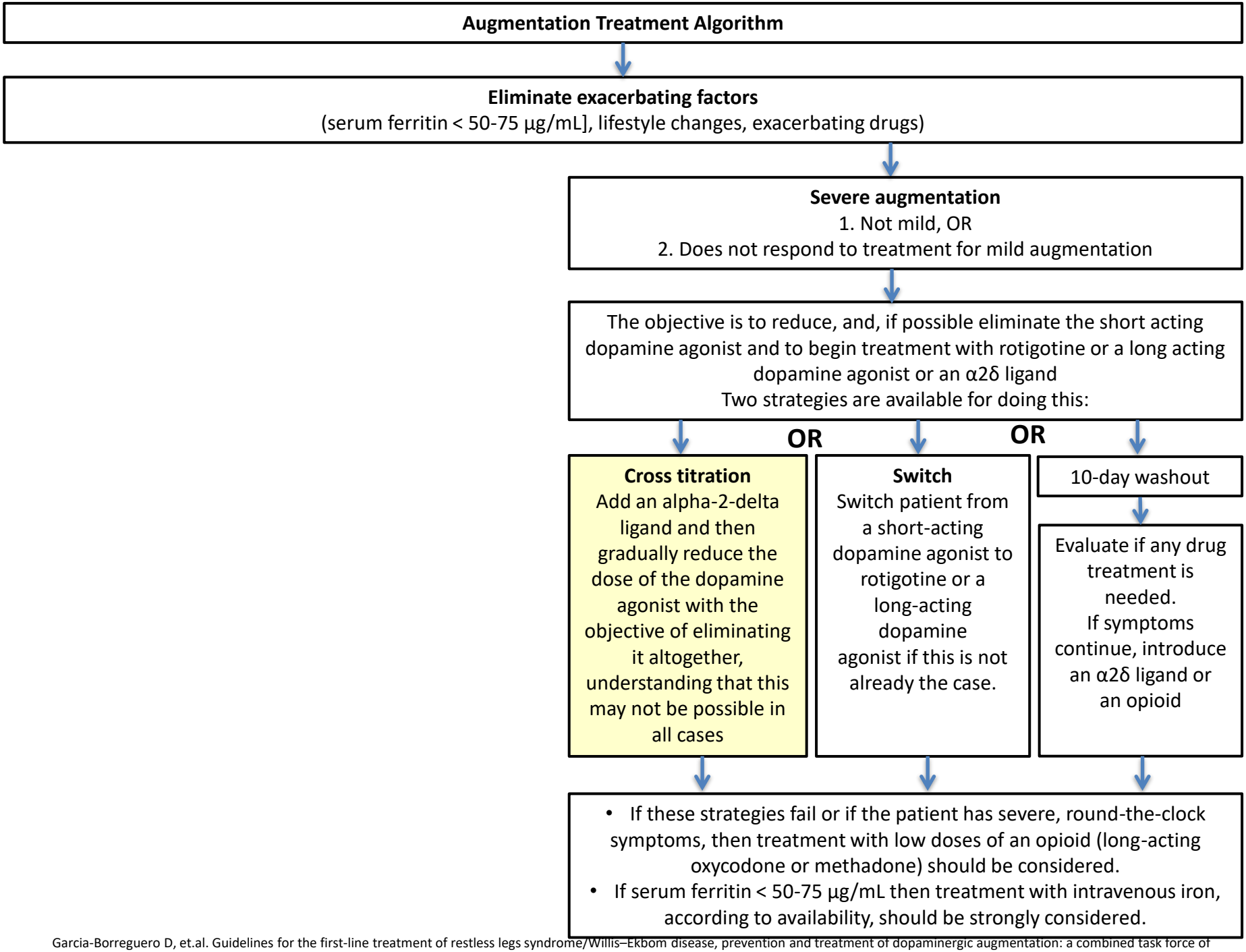

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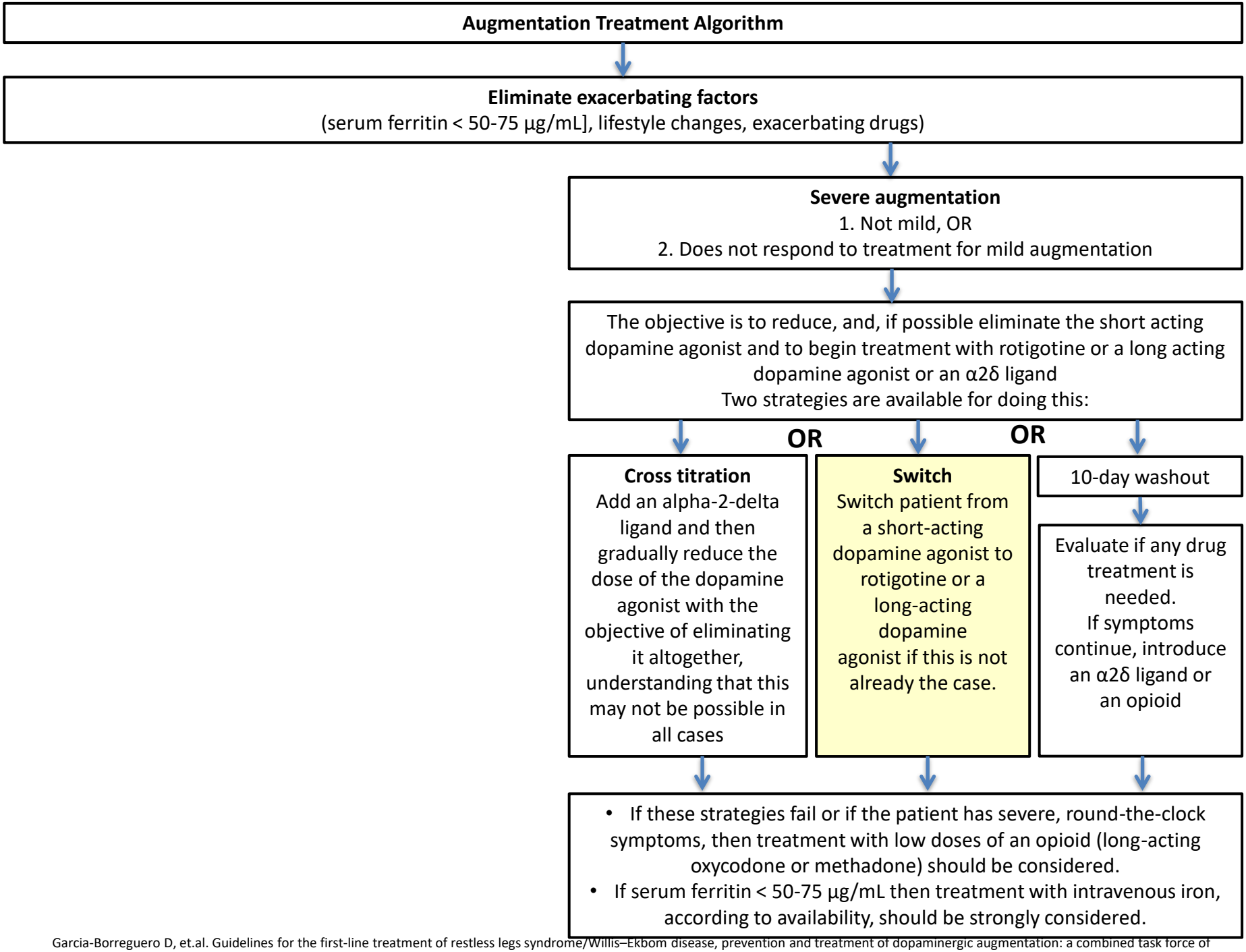

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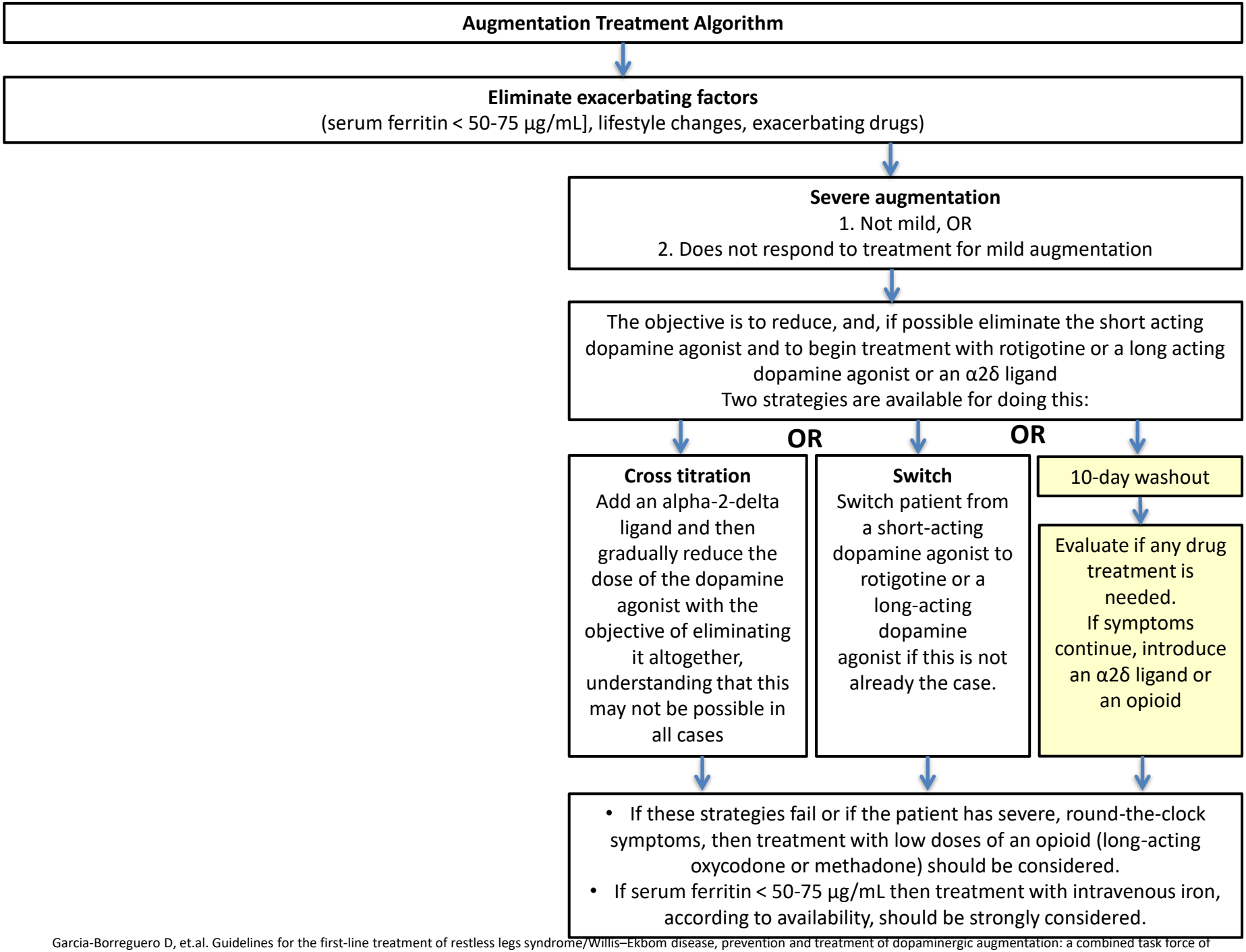

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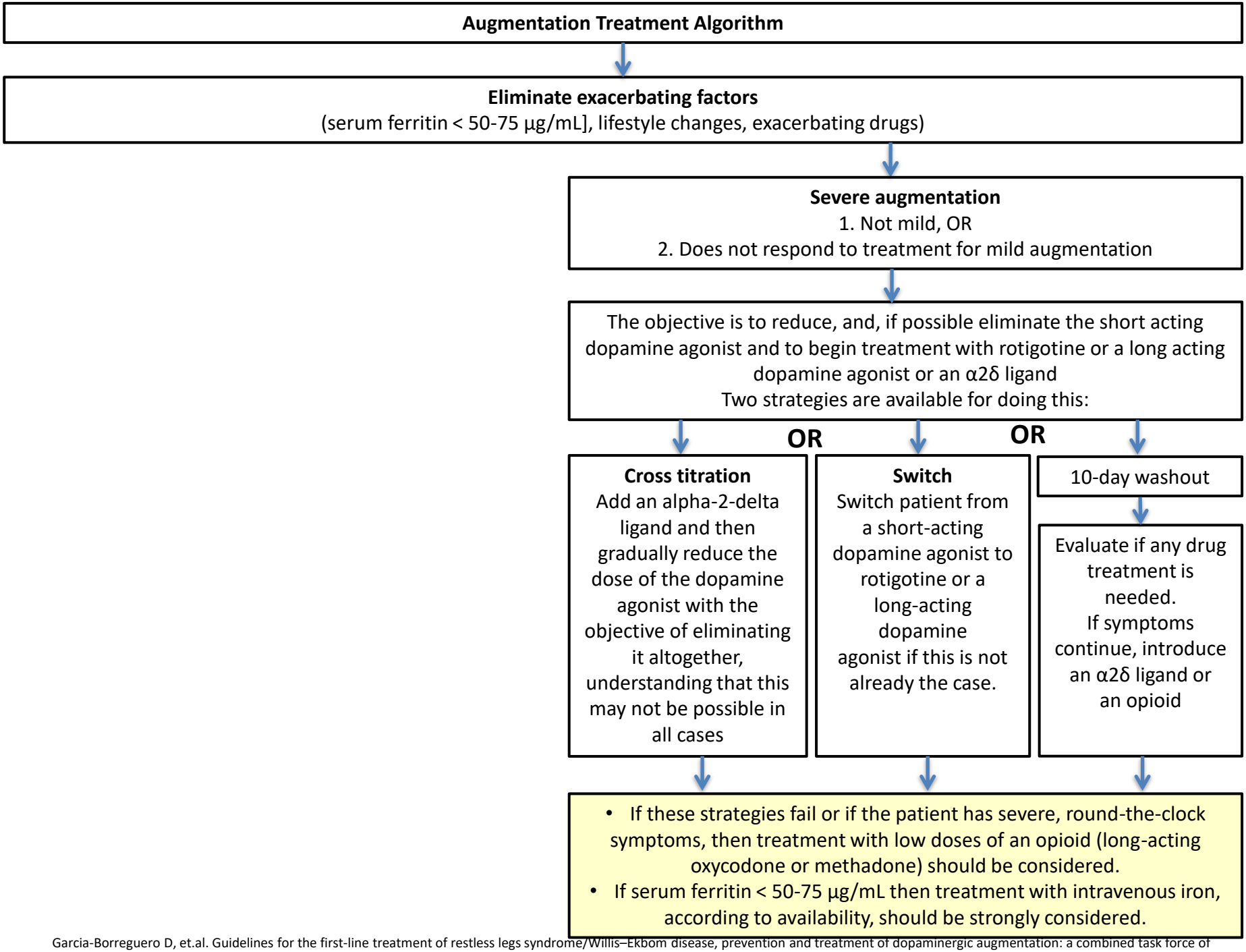

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Preventing Augmentation is much easier than Treating

- Check iron & ferritin levels
  - Transferrin saturation > 20%
  - Ferritin > 100 µg/mL
  - Consider IV iron infusions
    - LMW Iron Dextran (INFeD)
    - Ferric Carboxymaltose (Injectafer)
    - Ferumoxytol (Feraheme)

Preventing Augmentation is much easier than Treating

- Avoid starting short acting DA unless there are compelling reasons
- When prescribing short acting DA, keep the dose as low as possible
  - Pramipexole: start at .125 mg
  - Ropinirole: start at .25 mg
  - Start ½ tablet for > 65 years old

Preventing Augmentation is much easier than Treating

- Initiate treatment with an alpha-2-delta drug or long acting DA
  - Add the other class if necessary
  - Add opioids if needed
  - Consider intermittent DA therapy
    - Even Sinemet can be used up to 3X/week
    - Alternate DA with other therapies

RLS TREATMENT CONCLUSIONS

- Change your first line treatment of RLS
  - Avoid short-acting DA if possible
- Recognize augmentation
  - Think of augmentation whenever a patient on a DA asks for more medication or c/o worsened symptoms
- Treat RLS augmentation sooner rather than later
  - Do not keep increasing DA drugs
  - Do not change from one short acting DA to another
- Check iron & ferritin levels on all your RLS patients

Pediatric RLS REST Study

- 2% of children 8-17
- Moderate Sx - .5%
- Severe Sx – 1%
- No gender differences noted
- Negative effect on mood – 50%
- History of “growing pains” – 81%

Picchietti D, Allen RP, Walters AS, Davidson JE, Myers A, Ferini-Strambi L. Restless legs syndrome: prevalence and impact in children and adolescents--the Peds RESTstudy. Pediatrics. 2007 Aug;120(2):253-66.

Pediatric RLS Diagnosis

Sleep Medicine 14 (2013) 1253–1259

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Original Article

Pediatric restless legs syndrome diagnostic criteria: an update by the International Restless Legs Syndrome Study Group ☆

Daniel L. Picchietti [a,*], Oliviero Bruni [b], Al de Weerd [c], Jeffrey S. Durmer [d], Suresh Kotagal [e], Judith A. Owens [f], Narong Simakajornboon [g], On behalf of the International Restless Legs Syndrome Study Group (IRLSSG)

Picchietti DL, Bruni O, de Weerd A, Durmer JS, Kotagal S, Owens JA, Simakajornboon N; International Restless Legs Syndrome Study Group (IRLSSG). Pediatric restless legs syndrome diagnostic criteria: an update by the International Restless Legs Syndrome Study Group. Sleep Med. 2013 Dec;14(12):1253-9.

Pediatric RLS Diagnosis

Table 2
Special considerations for the diagnosis of pediatric restless legs syndrome.

- The child must describe the RLS symptoms in his or her own words
- The diagnostician should be aware of the typical words children and adolescents use to describe RLS
- Language and cognitive development determine the applicability of the RLS diagnostic criteria, rather than age
- It is not known if the adult specifiers for clinical course apply to pediatric RLS
- As in adults, a significant impact on sleep, mood, cognition, and function is found. However, impairment is manifest more often in behavioral and educational domains
- Simplified and updated research criteria for *probable* and *possible* pediatric RLS are available (Table 5)
- Periodic limb movement disorder may precede the diagnosis of RLS in some cases

Picchietti DL, Bruni O, de Weerd A, Durmer JS, Kotagal S, Owens JA, Simakajornboon N; International Restless Legs Syndrome Study Group (IRLSSG). Pediatric restless legs syndrome diagnostic criteria: an update by the International Restless Legs Syndrome Study Group. Sleep Med. 2013 Dec;14(12):1253-9.

Pediatric RLS Diagnosis

Table 5
Research diagnostic criteria for probable and possible pediatric restless legs syndrome.

Probable RLS
The child meets all five essential criteria for RLS, except criterion 4 (occurrence only or worsening in the evening or night)
Possible RLS
The child is observed to have behavior manifestations of lower extremity discomfort when sitting or lying, accompanied by motor movement of the affected limbs. The discomfort is characterized by RLS criteria 2–5 (is worse during rest and inactivity, relieved by movement, worse in the evening or night, and is not solely accounted for as primary to another medical or a behavioral condition)

Picchietti DL, Bruni O, de Weerd A, Durmer JS, Kotagal S, Owens JA, Simakajornboon N; International Restless Legs Syndrome Study Group (IRLSSG). Pediatric restless legs syndrome diagnostic criteria: an update by the International Restless Legs Syndrome Study Group. Sleep Med. 2013 Dec;14(12):1253-9.

Pediatric RLS Treatment

- Clonidine
- Clonazepam/other benzos
- Dopamine agonists
- Gabapentin (my drug of choice)
- Iron

RLS in Pregnancy

Sleep Medicine Reviews xxx (2014) 1–14

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CLINICAL REVIEW

Consensus clinical practice guidelines for the diagnosis and treatment of restless legs syndrome/Willis-Ekbom disease during pregnancy and lactation

Daniel L. Picchietti [a, *], Jennifer G. Hensley [b], Jacquelyn L. Bainbridge [c], Kathryn A. Lee [d], Mauro Manconi [e], James A. McGregor [f], Robert M. Silver [g], Claudia Trenkwalder [h, i], Arthur S. Walters [j], On behalf of the International Restless Legs Syndrome Study Group (IRLSSG)

Picchietti DL, Hensley JG, Bainbridge JL, Lee KA, Manconi M, McGregor JA, Silver RM, Trenkwalder C, Walters AS; International Restless Legs Syndrome Study Group (IRLSSG). Consensus clinical practice guidelines for the diagnosis and treatment of restless legs syndrome/Willis-Ekbom disease during pregnancy and lactation. Sleep Med Rev. 2015 Aug;22:64-77.

RLS in Pregnancy

- 15-25% of pregnant women
- Gender difference related to parity
  - Nulliparous women = men
- May be related to hormonal changes
- Peaks in 3rd trimester

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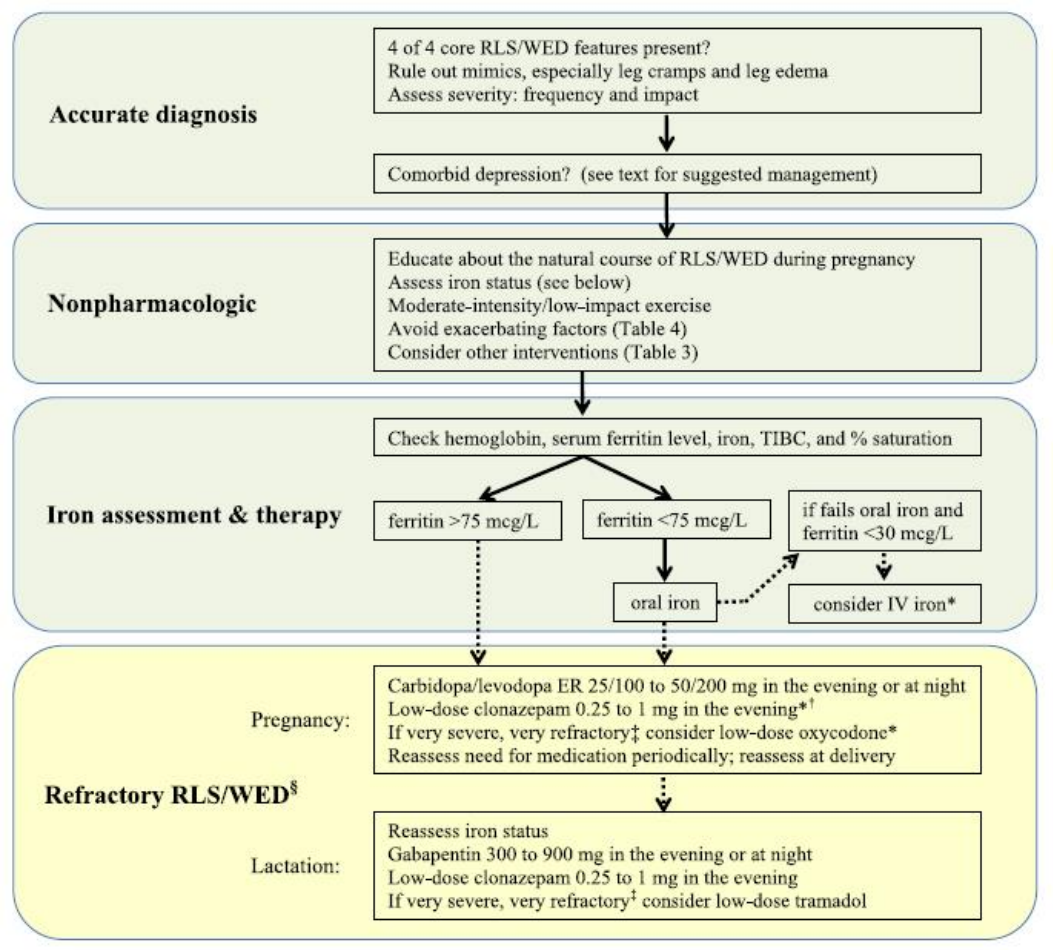
RLS Treatment in Pregnancy & Lactation



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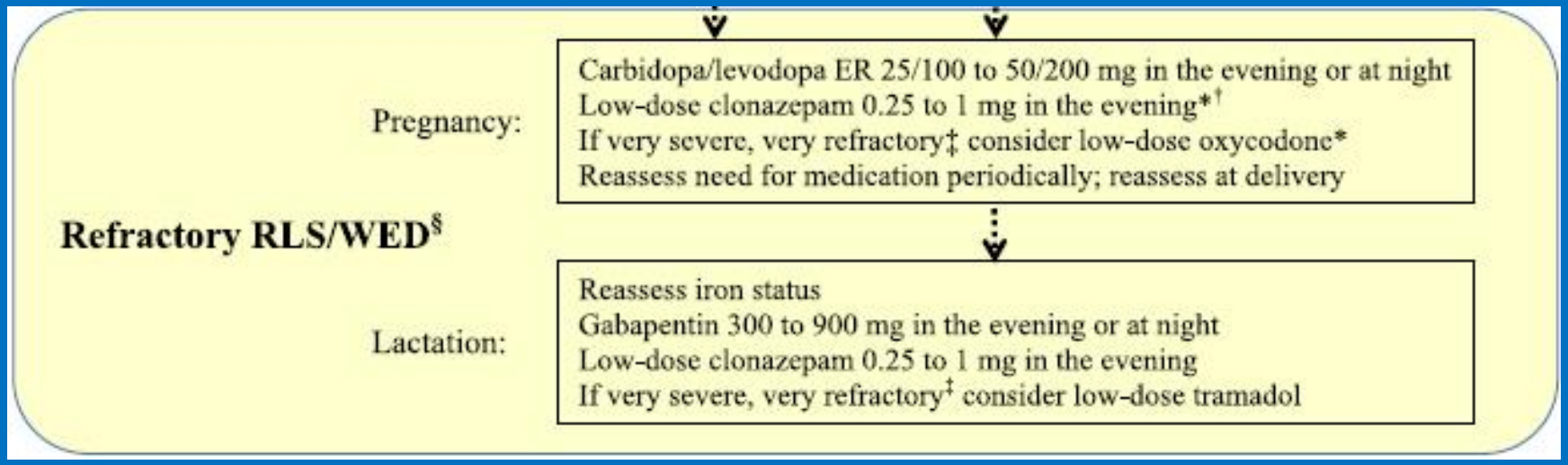

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Newer Medications?

- Adenosine system treatments
  - RLS associated with hypoadenosine states
  - Dipyridamole blocks the adenosine transporter
    - This increases extracellular adenosine
  - 2021 study showed improvement with dipyridamole
    - Dose range: 100 mg – 300 mg (mean dose 218 mg)

Garcia-Borreguero D, Garcia-Malo C, Granizo JJ, Ferré S. A Randomized, Placebo-Controlled Crossover Study with Dipyridamole for Restless Legs Syndrome. Mov Disord. 2021 Oct;36(10):2387-2392. doi: 10.1002/mds.28668. Epub 2021 Jun 17. PMID: 34137476

Garcia-Borreguero D, Guitart X, Garcia Malo C, Cano-Pumarega I, Granizo JJ, Ferré S. Treatment of restless legs syndrome/Willis-Ekbom disease with the non-selective ENT1/ENT2 inhibitor dipyridamole: testing the adenosine hypothesis. Sleep Med. 2018 May;45:94-97. doi: 10.1016/j.sleep.2018.02.002. Epub 2018 Feb 24. PMID: 29680437

Other Therapies?

- Marijuana
  - Very effective especially at bedtime
  - Only few puffs needed
- Diet
  - Low refined carbohydrates, gluten, ice cream
- Exercise
  - Mild to moderate helps, vigorous exacerbates
- Mechanical devices
  - Vibration
  - Neurostimulation