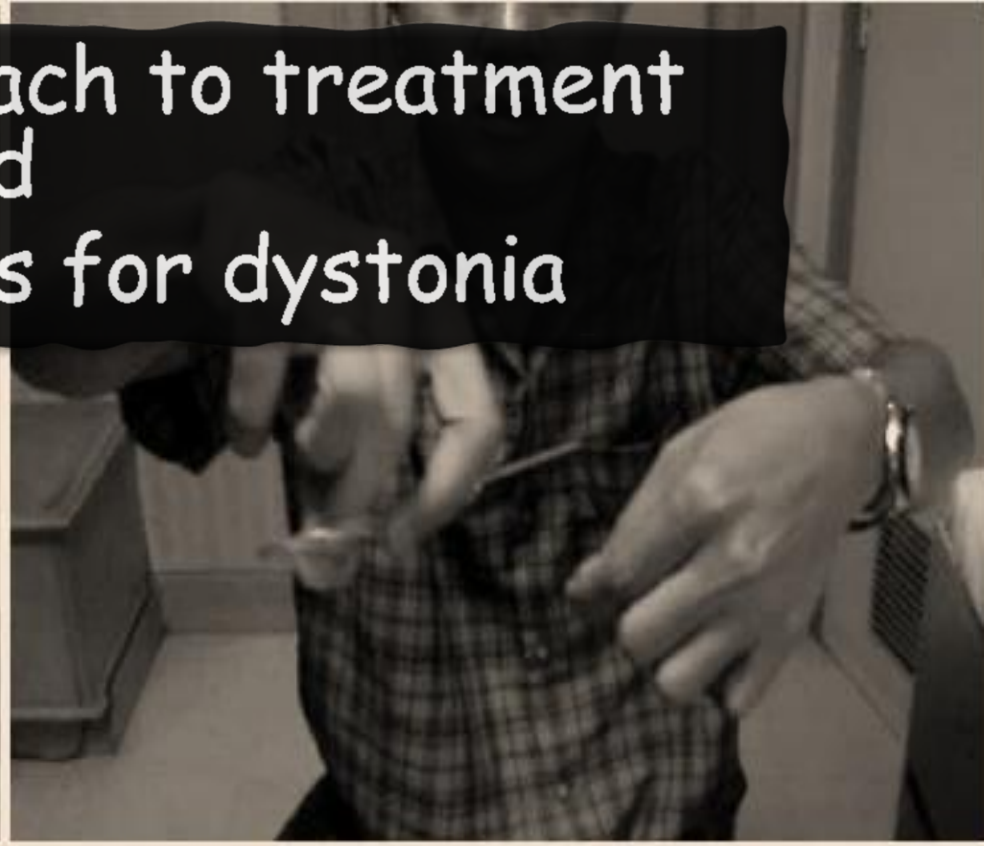
Algorithmic approach to treatment and oral medications for dystonia



Serhat Özkan

Treatment for Dystonia

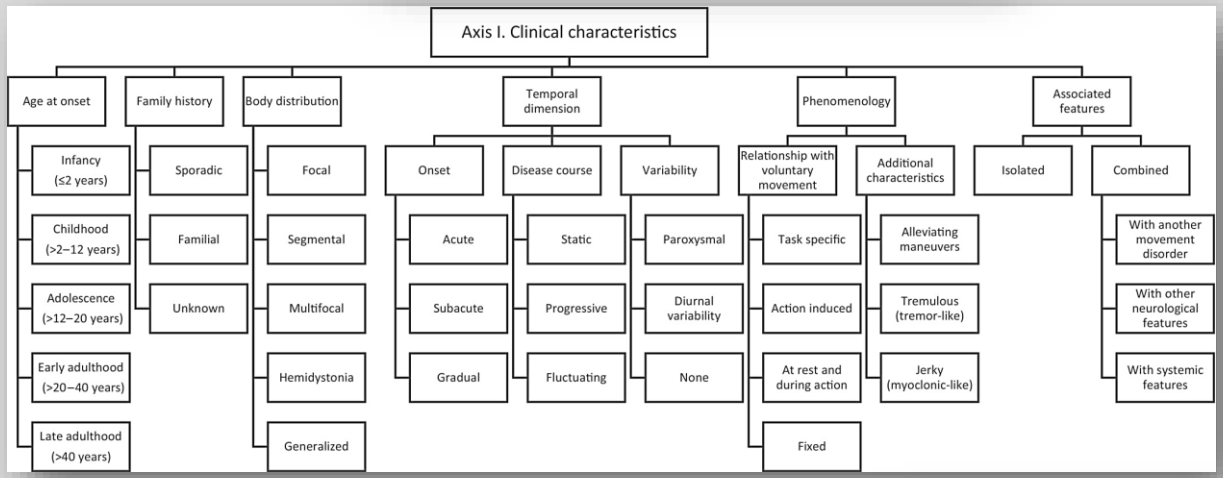
- Etiological Treatment
- Sypmtomatic Treatment
  - Botulinum toxin
  - Oral Medications
  - Surgery

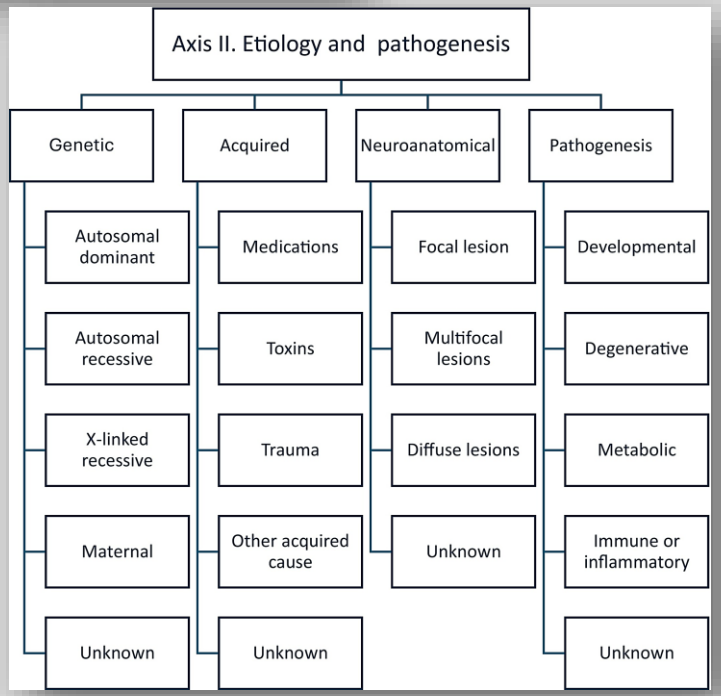
Physical Rehabilitation
&
Psychiatric Support

Phenomenology and Classification of Dystonia: A Consensus Update

Alberto Albanese, MD,[1,2*] Kailash Bhatia, MD, FRCP,[3] Susan B. Bressman, MD,[4] Mahlon R. DeLong, MD,[5] Stanley Fahn, MD,[6] Victor S.C. Fung, PhD, FRACP,[7] Mark Hallett, MD,[8] Joseph Jankovic, MD,[9] Hyder A. Jinnah, PhD,[10] Christine Klein, MD,[11] Anthony E. Lang, MD,[12] Jonathan W. Mink, MD, PhD,[13] Jan K. Teller, PhD[14]

Movement Disorders, Vol. 28, No. 7, 2013





Treatment Decision for Dystonia

- Hereditary or Acquired ?

  (Disease history, Family history, accompanying neurological / systemic signs-symptoms)

- Etiology ?

- Body parts that are involved ? *(Focal / Generelized, etc)*

- Onset age ?

  (infancy (≤2 years), childhood (>2–12 years), adolescence (>12–20 years), early adulthood (>20–40 years), and late adulthood (>40 years)

1. STEP

Right treatment needs Right Diagnosis

Is it Dystonia ???

- **sustained or intermittent muscle contractions**
- causing **abnormal movements, abnormal postures**, or both

- **typically patterned**, twisting, may be tremulous.

(e.g. Myoclonic, choreic)

- **often initiated or worsened by voluntary action** and associated with overflow muscle activation

Consensus Update Albanese et al Mov Disord 2013

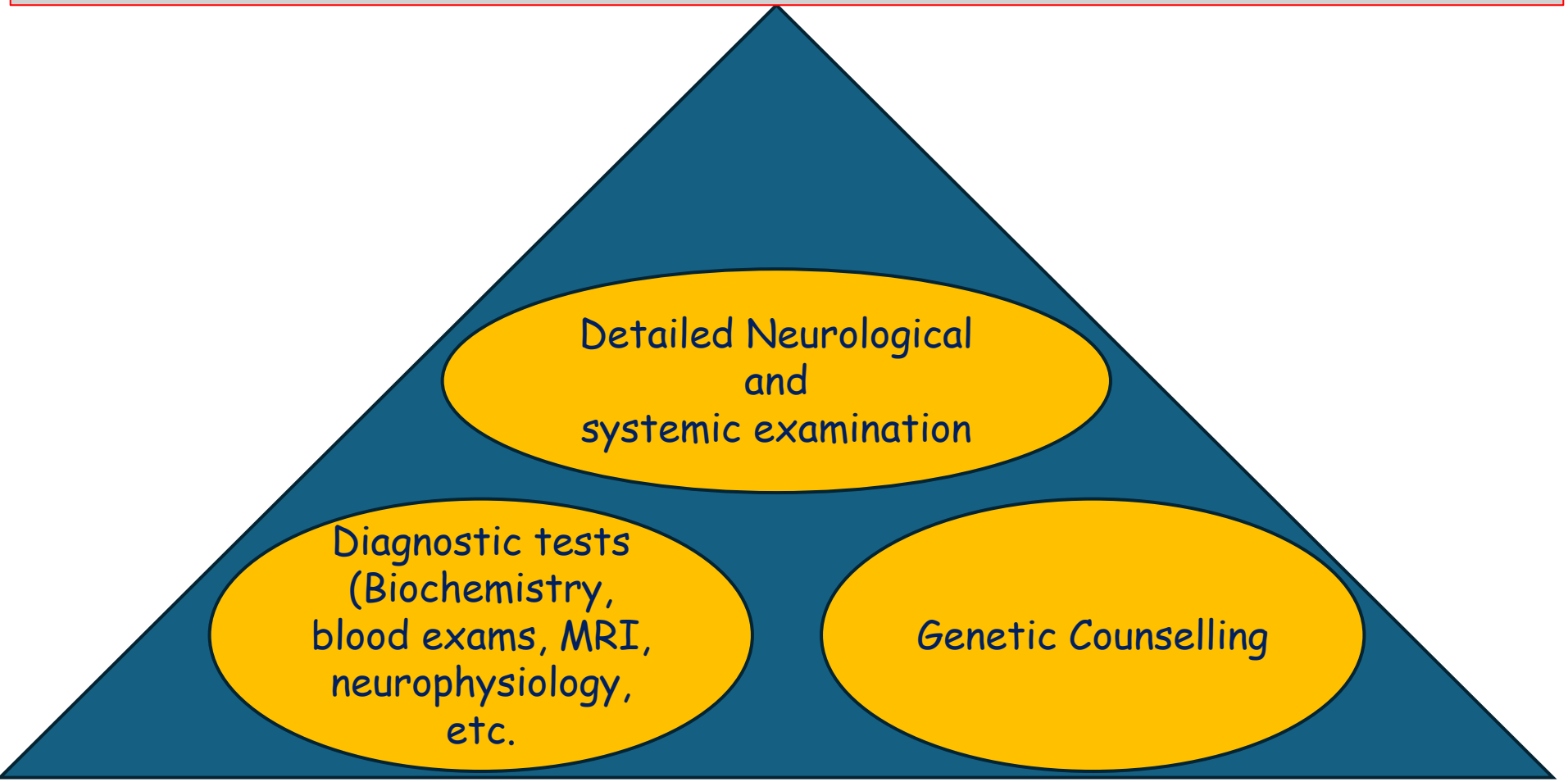
Exclude pseudodystonia
and
functional dystonia

rapid onset, fixed postures
inconsistency
variability on exam
Extreme pain, etc

Psychiatric Consuelation

2. STEP

Does the patient have a tretable etiology for dystonia ???



2. STEP

Does the patient have a tretable etiology for dystonia ???

Identify treatable dystonia:

Acquired Dystonias

- ✓ Levodopa-induced dystonia,
- ✓ Tardive dystonia,
- ✓ Cerebral palsy,
- ✓ Cerebral infections,
- ✓ Stroke,
- ✓ Brain tumor,
- ✓ Toxicants such as manganese, cyanide, etc

Neurodegenerative disease
(PKAN, CBS, MSA, PSP, etc.)

Neurometabolic disorders

Heavy metal-related disorders
(Wilson's disease, Neuroferritinopathies)

Does the patient have a tretable etiology for dystonia ???

Identify treatable dystonia:

Neurometabolic disorders

- Seizure ; MMR
- Loss of developmental skills
- Muscle weakness, Ataxia
- Vision problems (such as retinal abnormalities, cataracts)
- Hearing problems
- Abnormal head growth (such as macrocephaly or microcephaly)
- PNP
- Organomegalies

Heavy metal-related disorders (Wilson's disease, Neuroferritinopathies)

- Abnormal Biochemical abnormalities
- Eye, skin, organopathy signs
- Brain MRI; Genetic

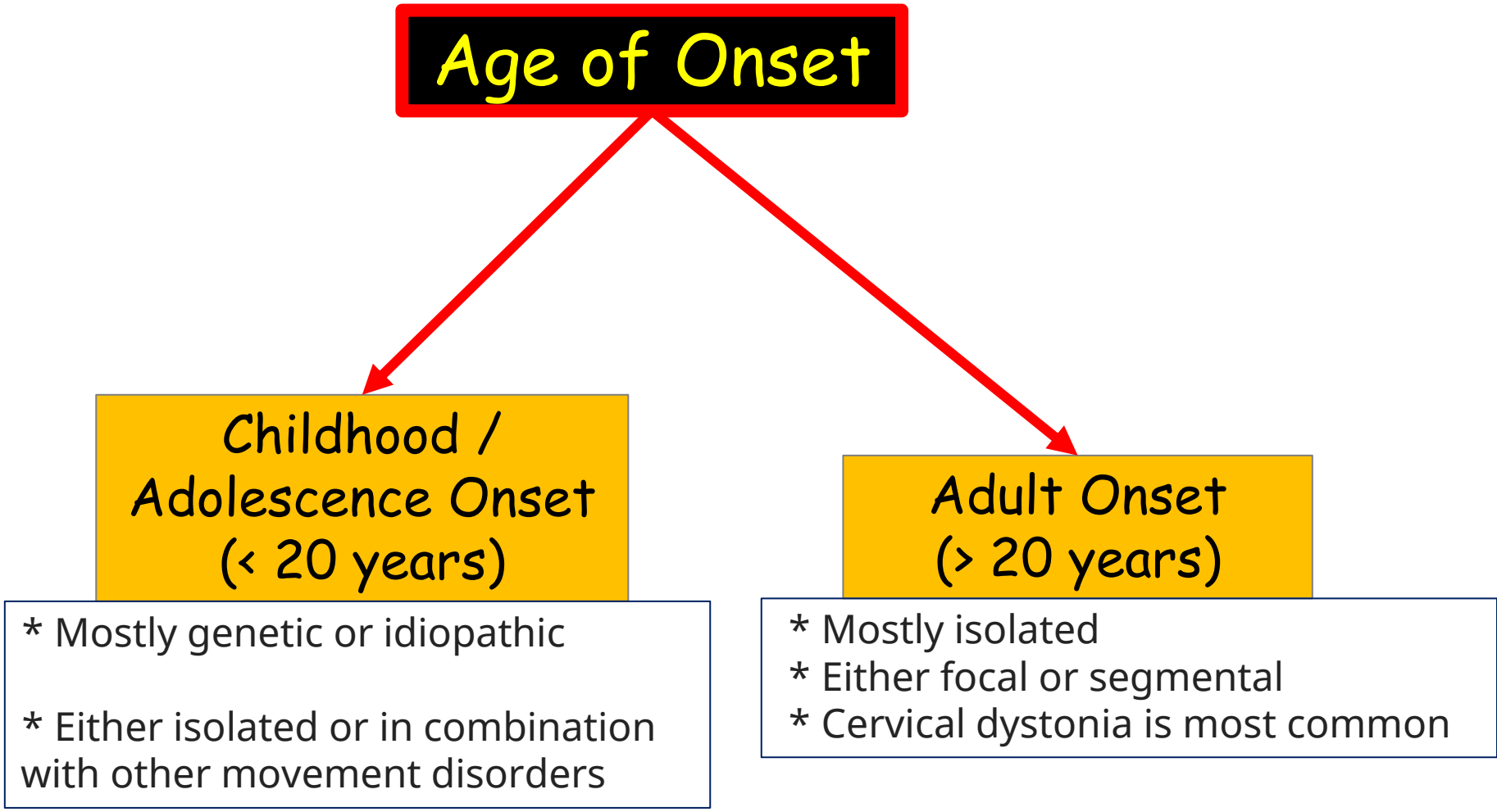
Disorder	Gene(s)	Diagnostic tests	Treatment
Dopa-responsive dystonia, classic	GCH1	•Levodopa challenge •CSF pterins and biogenic amines •Genetic testing	Levodopa
Dopa-responsive dystonia, complex	TH, PTPS, SPR	•Levodopa challenge •CSF HVA, 5-HIAA, and sepiapterin •Genetic testing	Levodopa, 5-hydroxytryptophan, or tetrahydrobiopterin
Dystonia with brain manganese deposition	SLC30A10, SLC9A14	•Serum manganese and iron •Peripheral blood smear •Genetic testing	Chelation therapy
Glucose transporter type 1 deficiency	SLC2A1	•Serum and CSF glucose •Genetic testing	Ketogenic diet or triheptanoin
Rapid-onset dystonia-parkinsonism	ATP1A3	•CSF HVA	Avoid or treat intercurrent illness to prevent encephalopathic crises
Wilson disease	ATP7B	•Slit lamp examination •Plasma copper and ceruloplasmin •24-hour urine copper	Zinc or tetrathiomolybdate
ADCY5-related dyskinesia	ADCY5	•Genetic testing	Caffeine

3. STEP

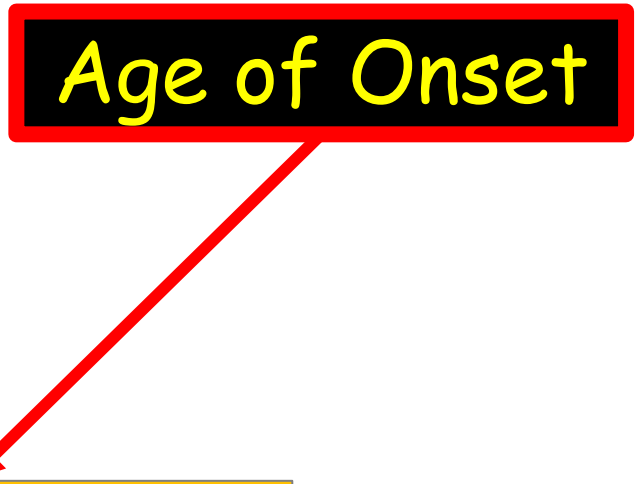
Sypmtomatic Treatment of Dystonia

- Botulinum Toxin Injections
- Oral Medications
- Surgery
    * DBS
    * Ablative surgery
    * Denervation
    * Intrathecal Baclofen

What treatment modality or modalities should be initiated?



What treatment modality or modalities should be initiated?



Childhood / Adolescence Onset (< 20 years)

* Mostly genetic or idiopathic

* Either isolated or in combination with other movement disorders

Childhood / Adolescence Onset (< 20 years)

(For children with isolated, idiopathic focal or generalized dystonia)

First treatment attempt

Levodopa trial

5% to 10% of dystonias that begin in childhood are dopamine-responsive dystonias (DRDs)

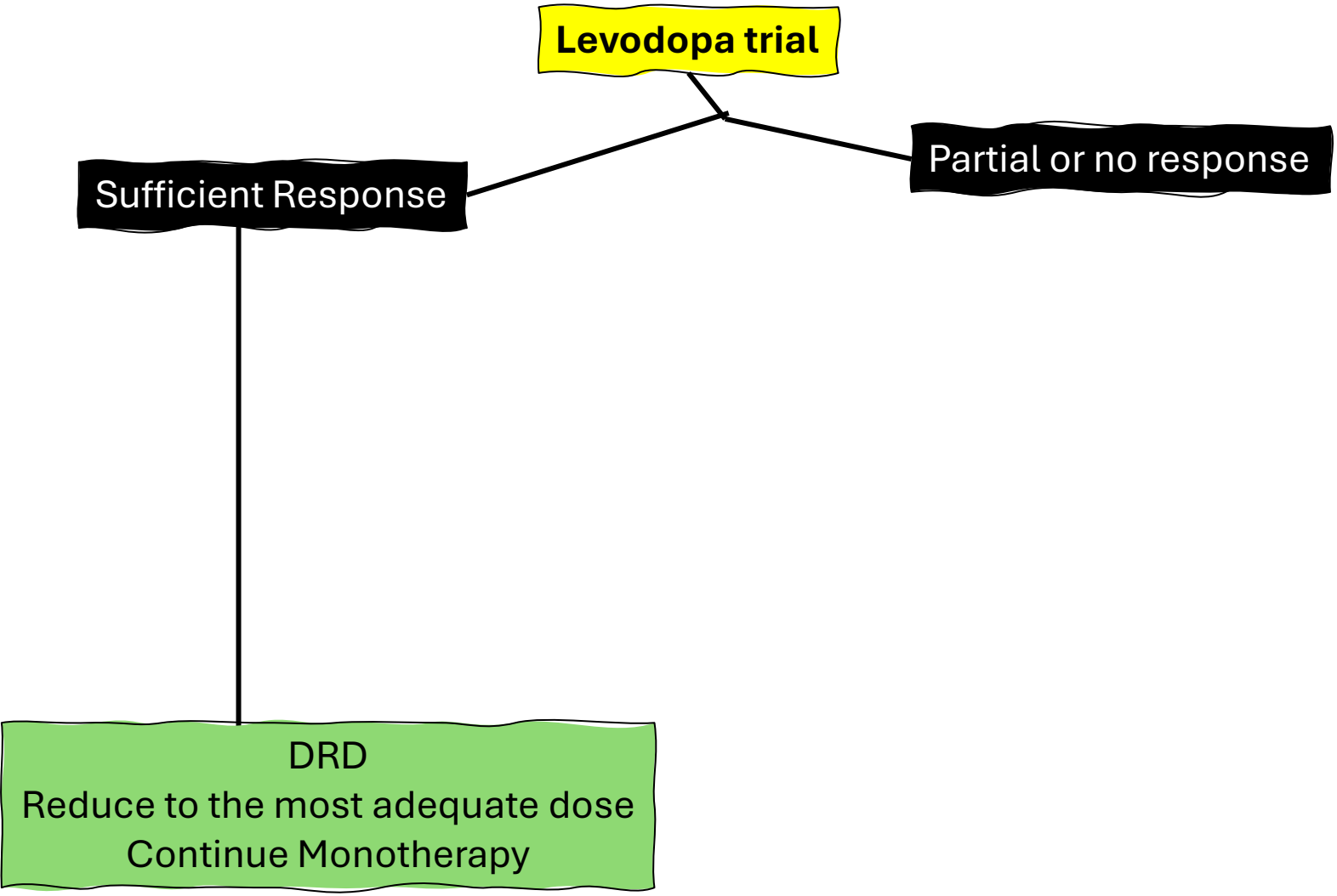
- Begin 1 mg/kg/day, divided dosage (2 times a day) (one week)
- Increase every week 3- 5 mg/kg/day (3 times a day)
- 20 mg/kg/day daily dose (3 x 100 mg), 3 monthes

** Up to 400-600 mg of levodopa daily in adults*

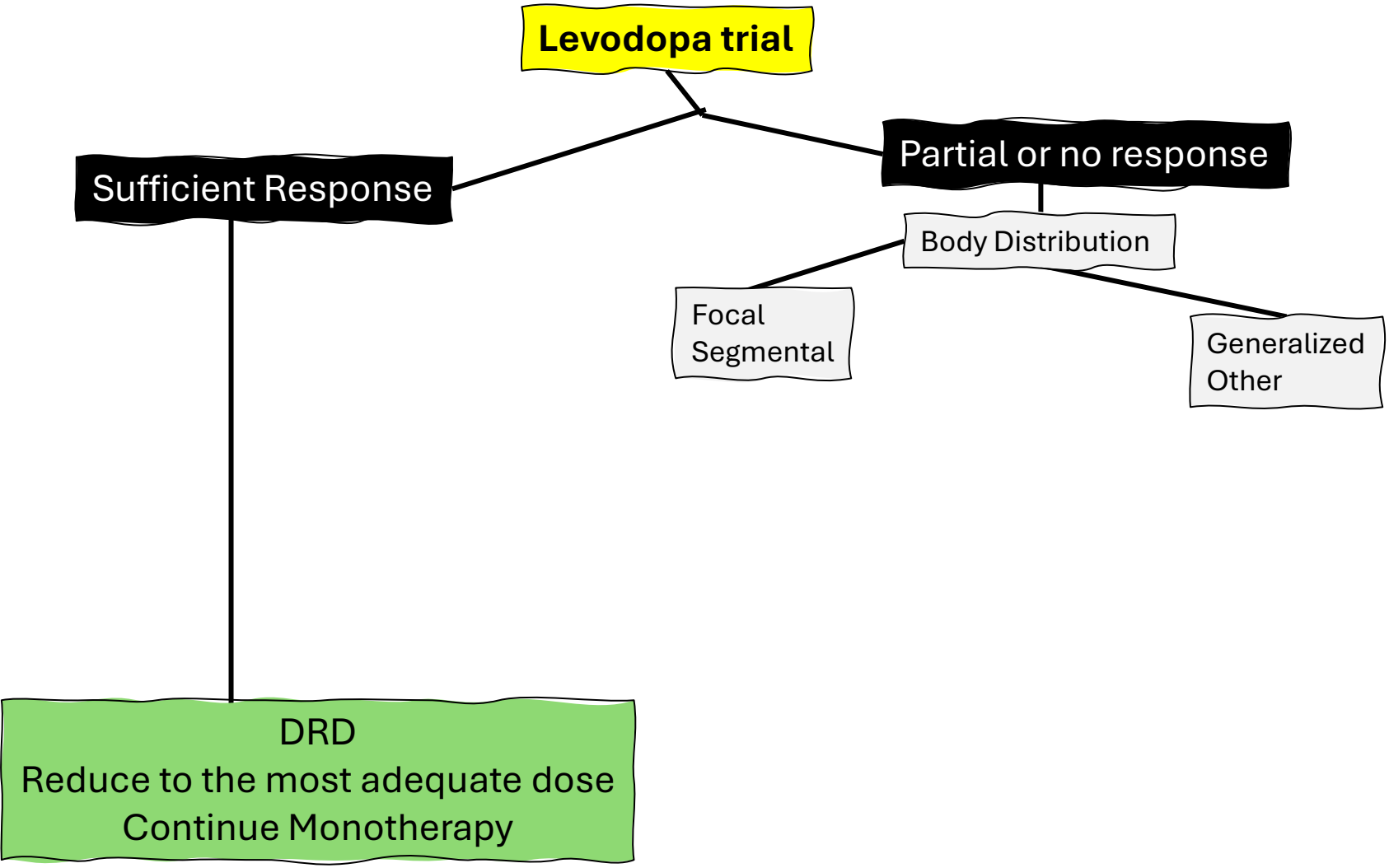
Higher doses is not recomended without genetic results

Pract Neurol. 2015;15:340–5

Childhood / Adolescence Onset (< 20 years)



Childhood / Adolescence Onset (< 20 years)



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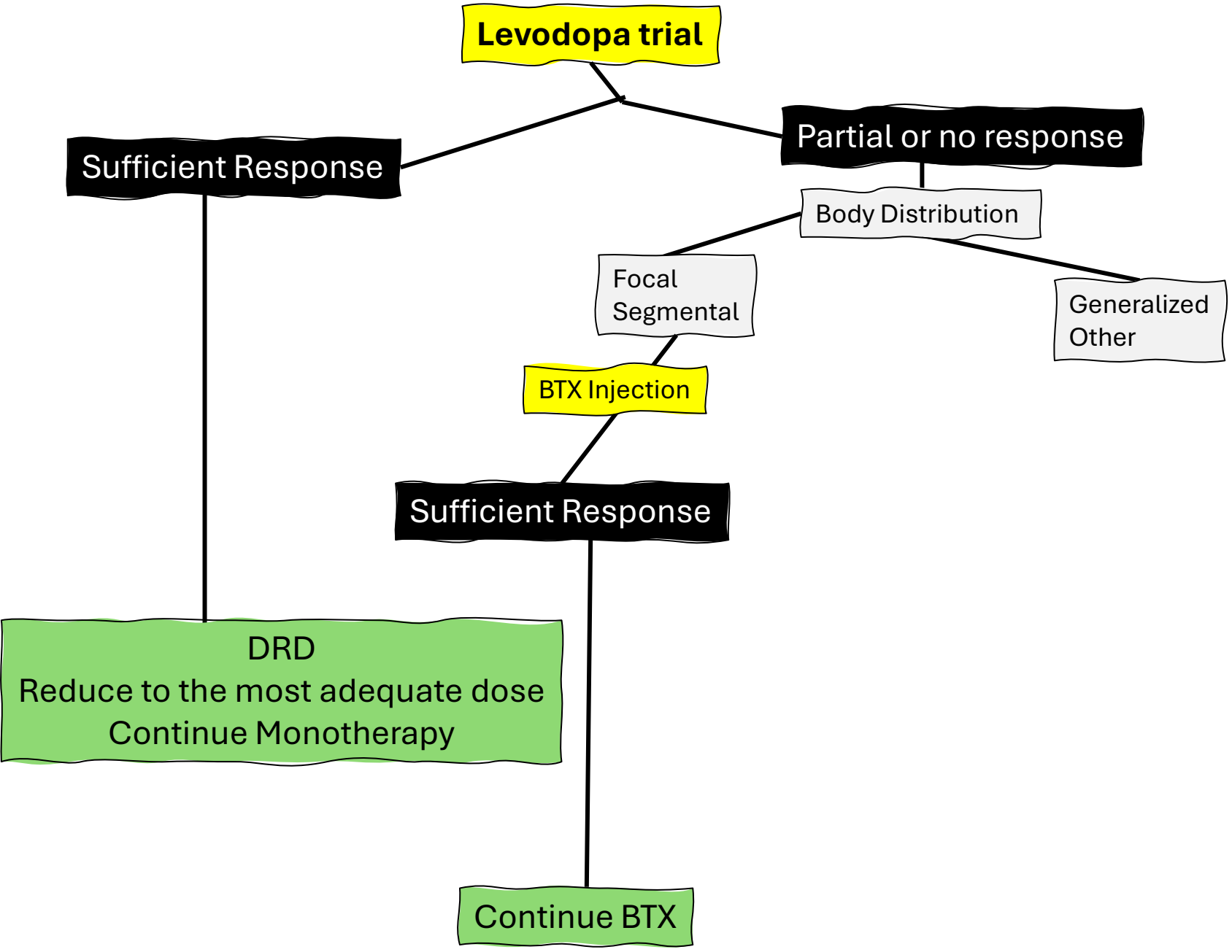
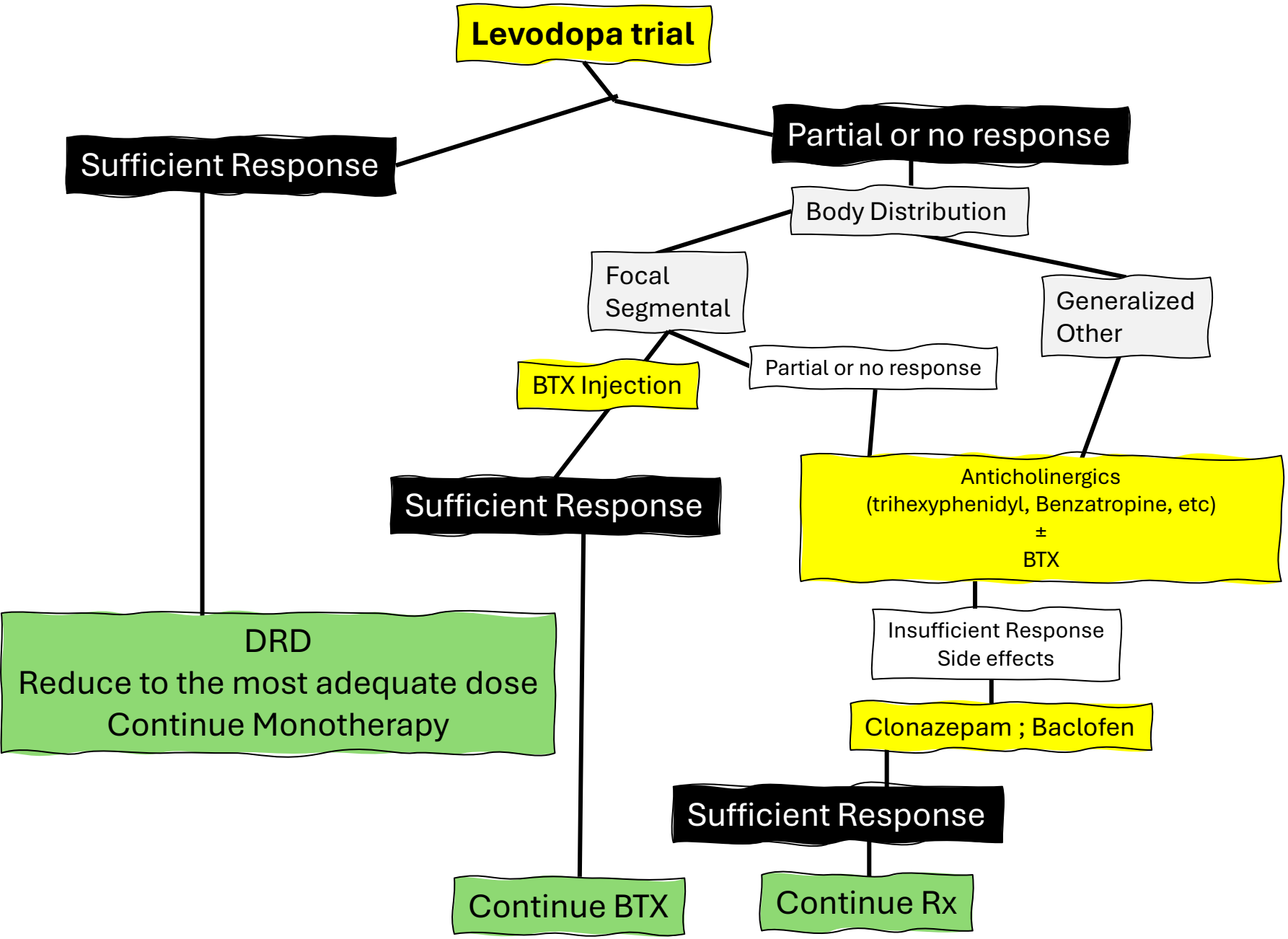
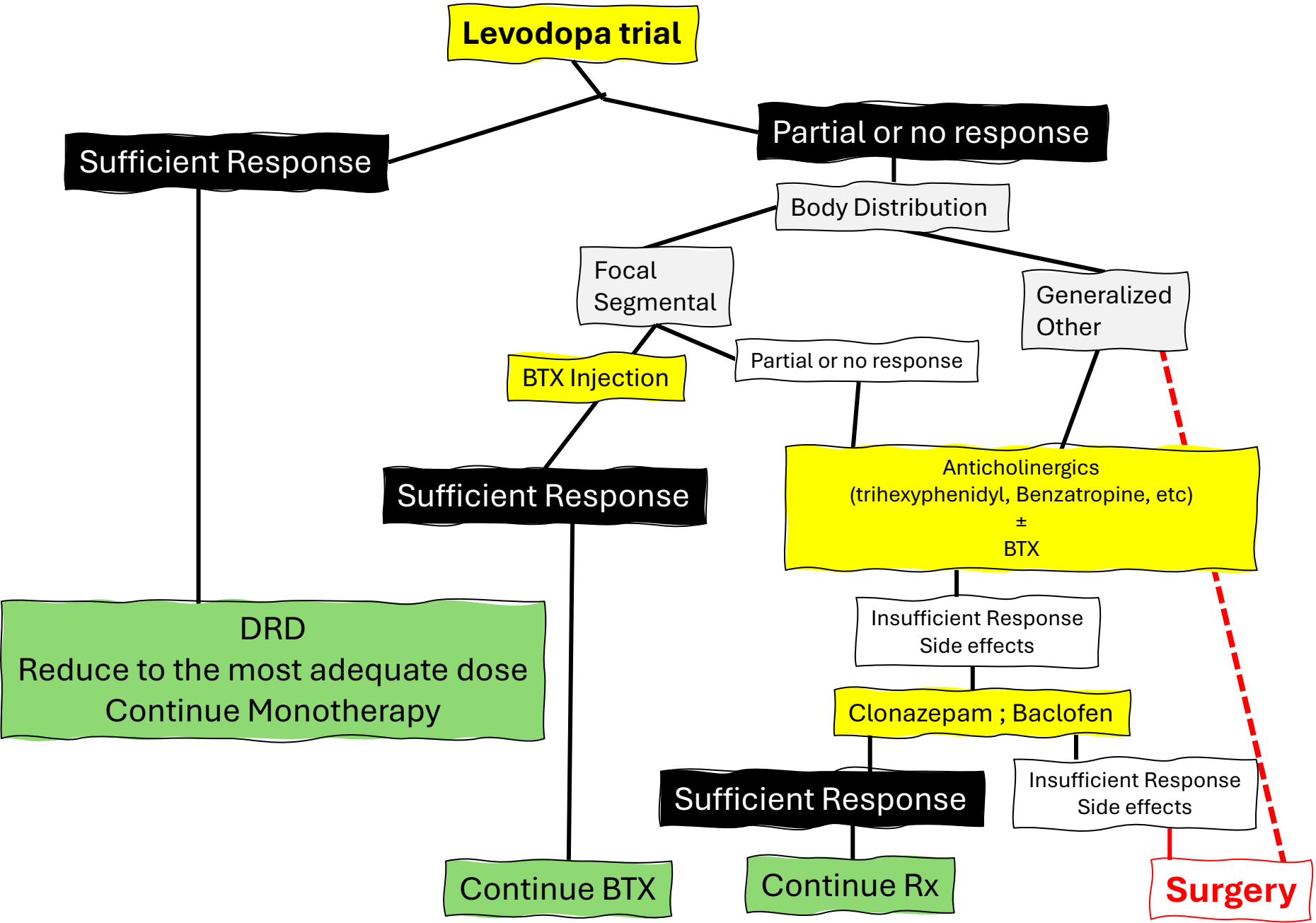


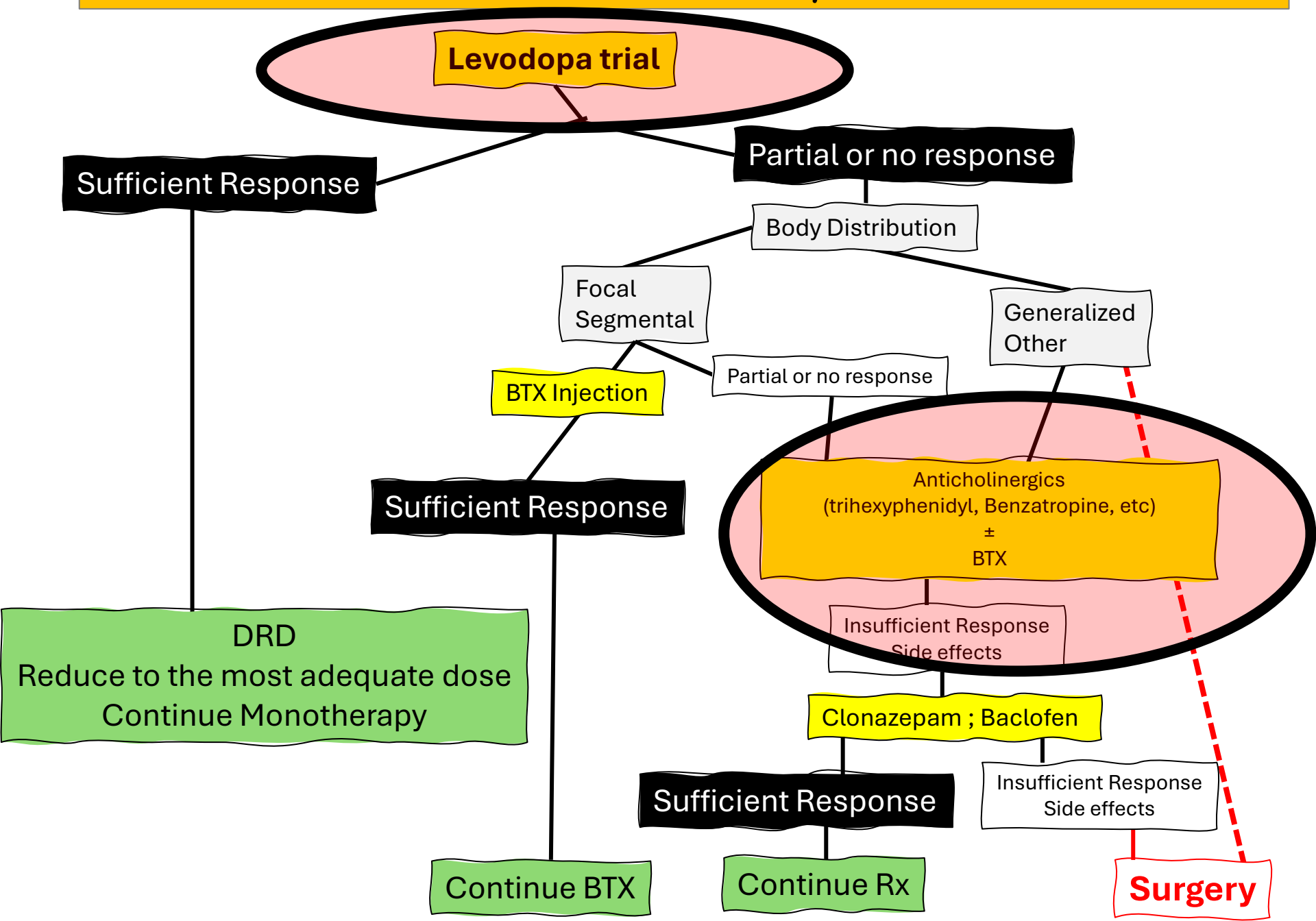
Childhood / Adolescence Onset (< 20 years)



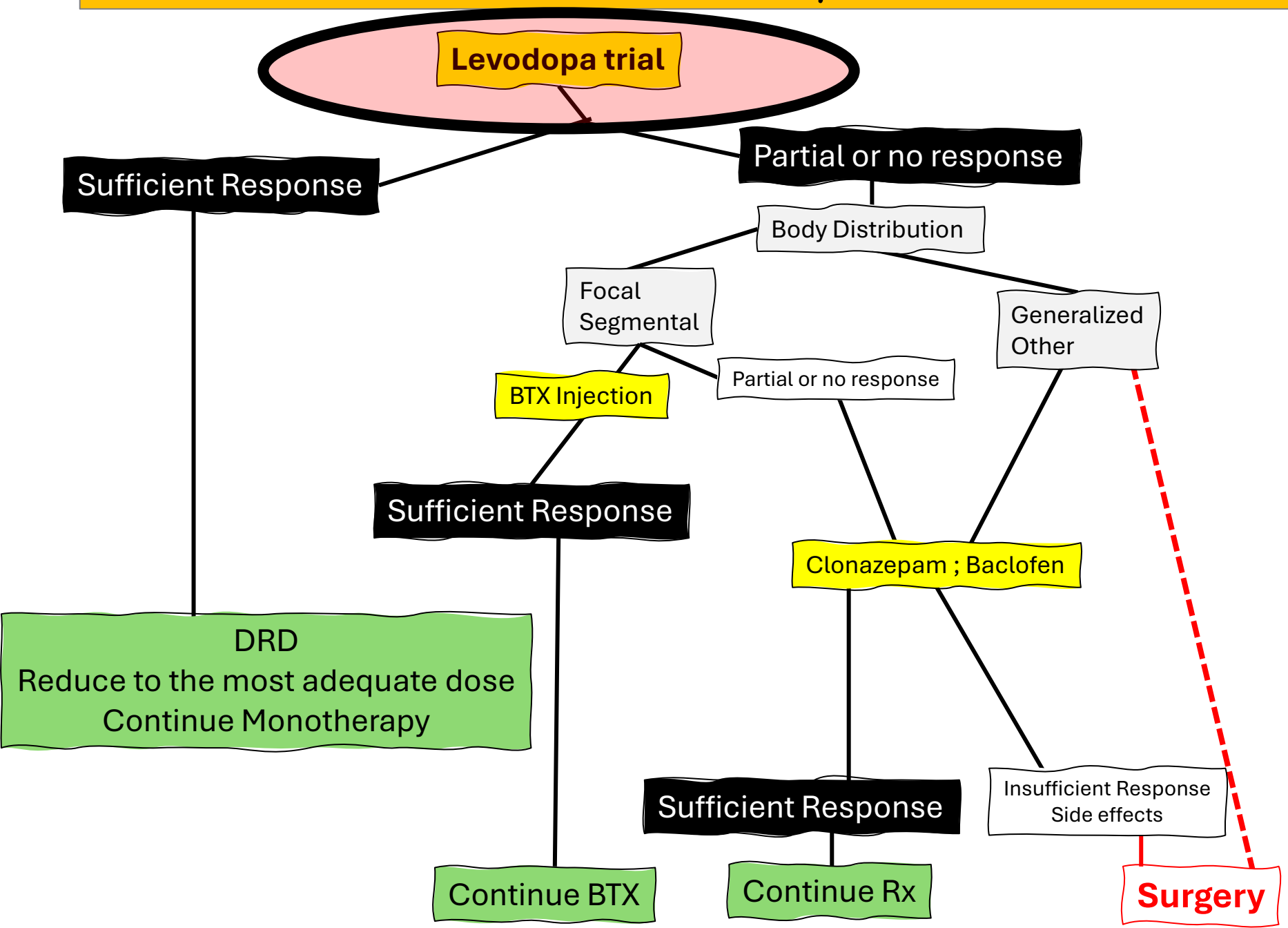
Childhood / Adolescence Onset (< 20 years)



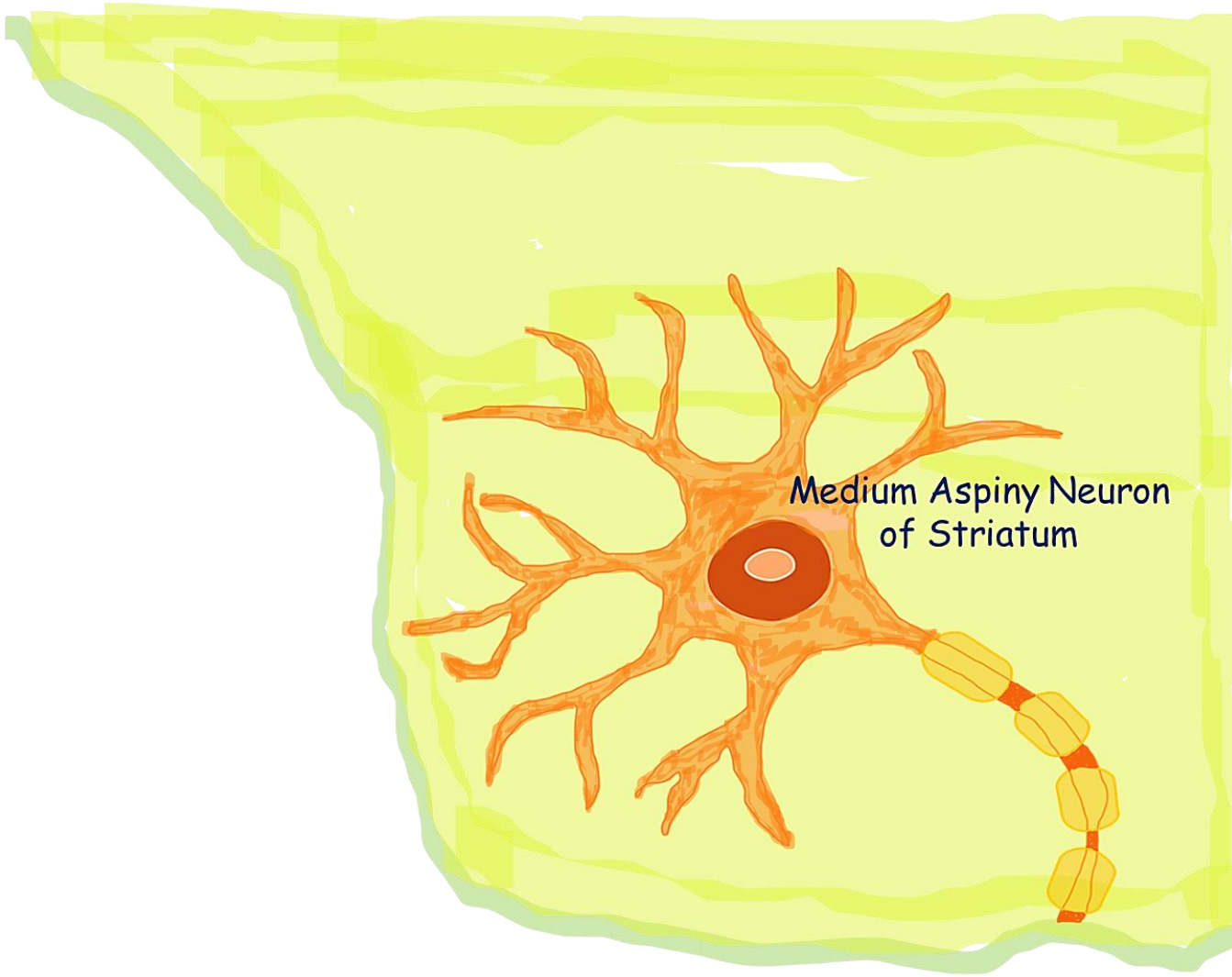
Adult Onset (> 20 years)



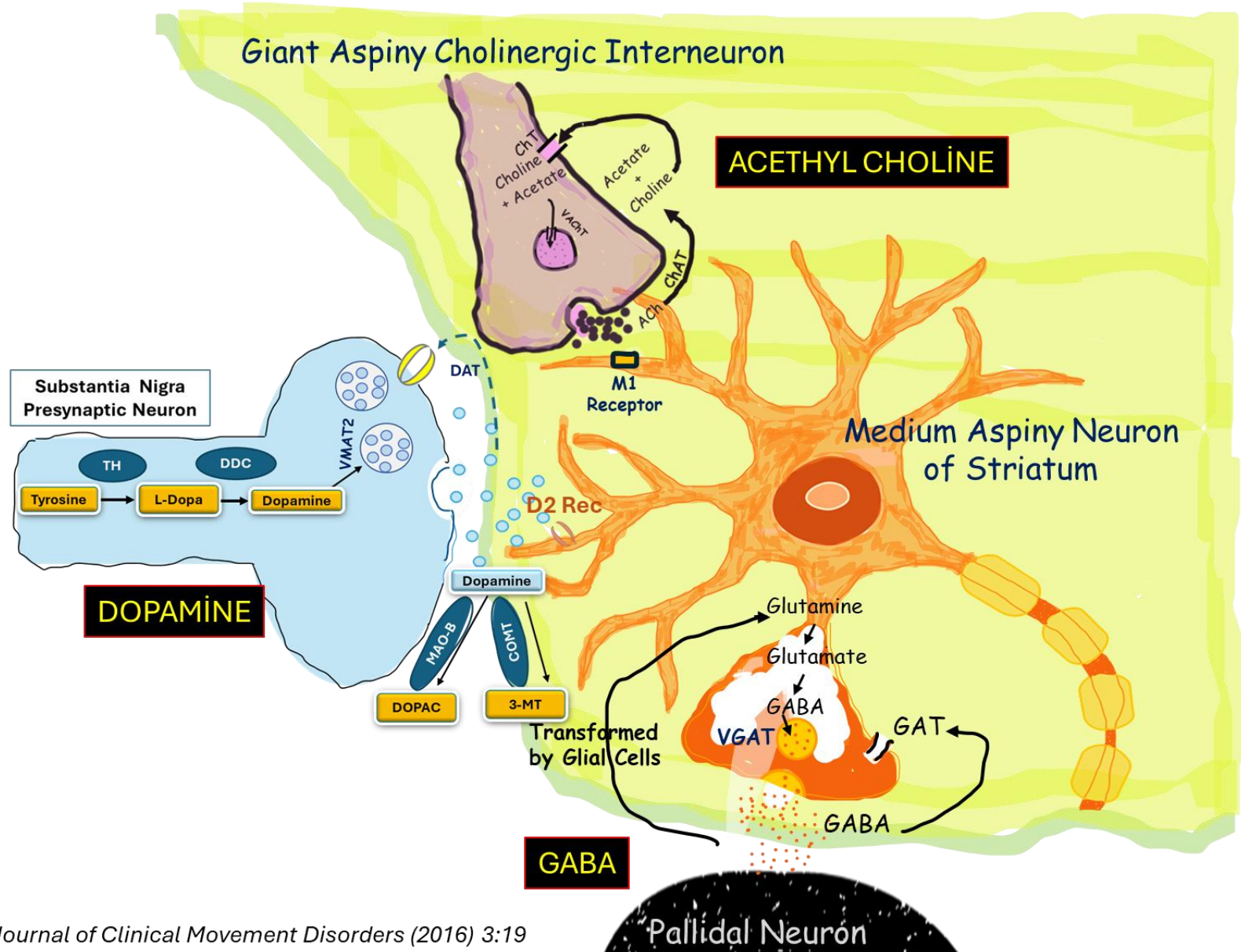
Adult Onset (> 20 years)



Oral Medications for dystonia



Oral Medications for dystonia



Journal of Clinical Movement Disorders (2016) 3:19

Oral Medications for dystonia

Most of evidence for these agents are from open-label prospective studies, case reports, case series, and retrospective studies

Fahn principle; "*start low and go slow*."

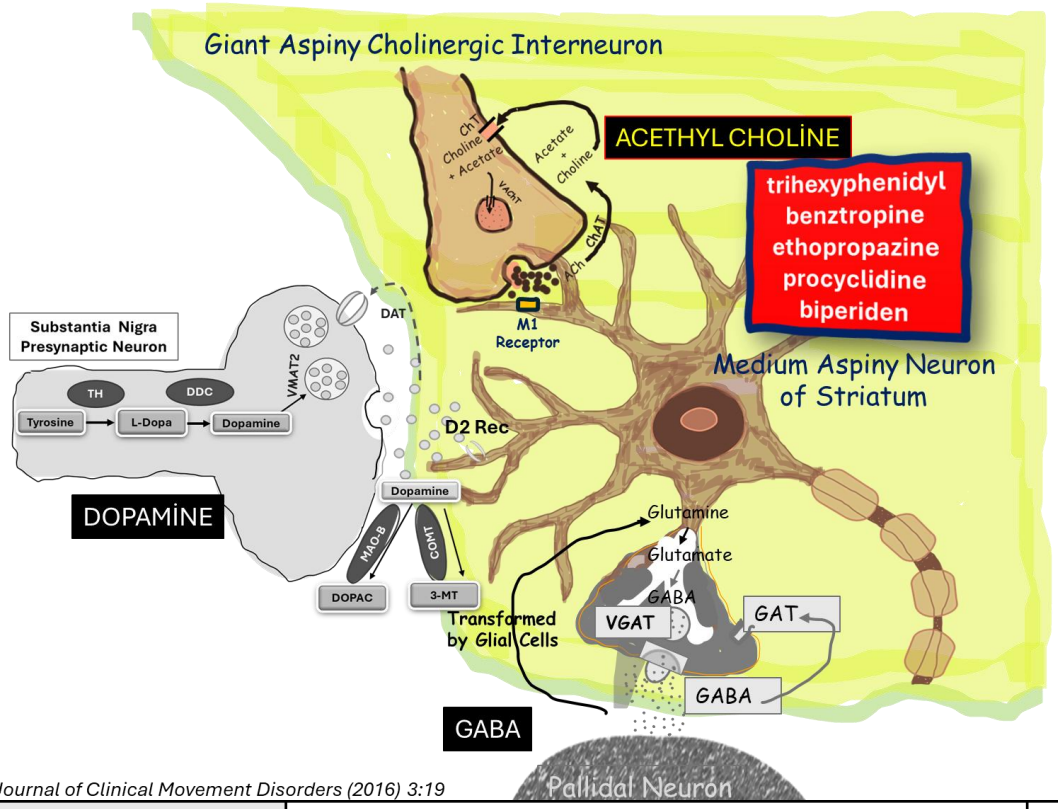
Start at the minimum dose
Titrate in small increments until sufficient symptom control
With the least bothersome side-effects

Titration for children every 3 to 4 days
For adults every 7 days

2-4 week observation period
Intolerable side effects, downtitration of the dose

Can J Neurol Sci. 1987;14(3 Suppl):528-532

Anticholinergics for dystonia



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Trihexyphenidyl, **Biperiden, Benzatropine** *(Acute tardive syndromes)* Procyclidine; Diphenhydramine; Ethopropazine	* ~ 40 % effect on early onset patients (Child onset) • Side effects is the major problem • Slow titration * Early treatment, better results	Dry mouth; Impaired vision; **Glaucoma -;** **Urinary retention;** **Cognitive problems**; **Hallucinations;** Sedation; **Cardiac block**

Trihexyphenidyl

- *Trihexyphenidyl 5 mg tab.; Artane 2 mg tab.*

Torsion dystonia: a double-blind, prospective trial of high-dosage trihexyphenidyl

R E Burke, S Fahn, C D Marsden

PMID: 3511401 DOI: 10.1212/wnl.36.2.160

Abstract

We studied trihexyphenidyl in the treatment of torsion dystonia in a prospective, double-blind crossover protocol. Thirty-one patients completed the protocol. Twenty-two (71%) had a clinically significant response. After a mean follow-up of 2.4 years, 68% of patients continued to take trihexyphenidyl, and 42% continued to show a considerable or dramatic benefit. The 30-mg dose used was generally well tolerated. High-dosage trihexyphenidyl therapy is effective in the management of torsion dystonia.

Neurology 1986 Feb;36(2):160-4.

Dry mouth;
Nausea;Vomiting;
Impaired vision;
Urinary retention;
Cognitive problems;
Hallucinations;
Sedation

31 patients (9 – 32 years old)
71% response
30 mg/day average dosage

Younger patients tolerate better

Withdrawal effects; anxiety, tachycardia, orthostatic hypotension, insomnia

Trihexyphenidyl

- At least 12 to 100 mg / day

- Starting with 1 mg at bedtime
- Slow titration
- 1–2 mg per week, increasing to 12 mg/day, divided across 3–4 doses

Biperiden

- *Akineton 2 mg tab.*

> Clin Neurol Neurosurg. 1991;93(1):35-7. doi: 10.1016/0303-8467(91)90006-b.

High dose anticholinergic therapy (biperiden) in dystonia

N S Oztekin [1], S S Saygi, T Dalkara, I Senses, T Zileli

Affiliations + expand

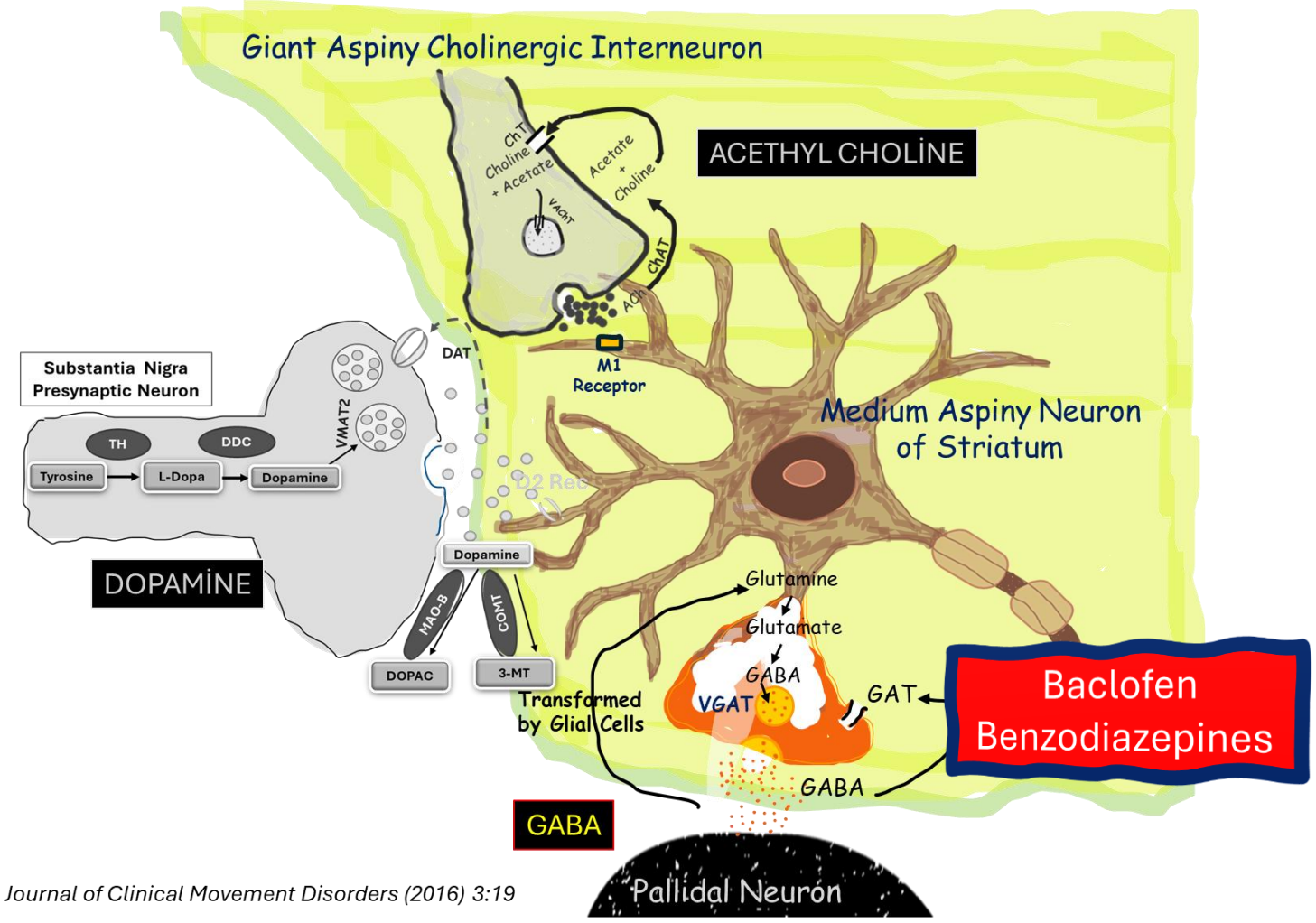
PMID: 1651189 DOI: 10.1016/0303-8467(91)90006-b

Abstract

We studied the effect of biperiden in the treatment of dystonia in six patients aged 15-30 years. Five patients had generalized and one patient had segmental dystonia. Biperiden was started at a dose of 2 mg/day and was gradually increased to 40 mg/day in a few weeks. All patients had clinically significant response in varying degrees after a mean follow up of 1.9 years. Three patients showed considerable or dramatic benefit. The 40 mg/day was generally well tolerated. High dose anticholinergic therapy is effective in the management of torsion dystonia.

Acute Iatrogenic Dystonia
Tardive Dystonia

GABAergics for dystonia



Journal of Clinical Movement Disorders (2016) 3:19

Baclofen

- $GABA_b$ receptor agonist
- Efect < Anticholinergics
- Generelized Dystonia in extremity located dystonias with spasticity
- **Cp / Distonia +**

- PO or Intrathecal infusion

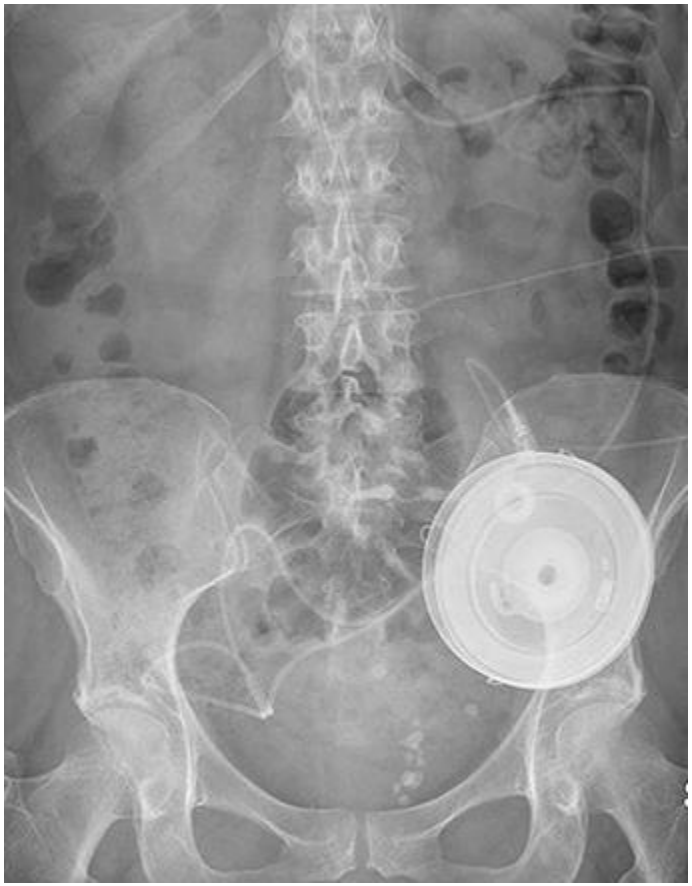
Baclofen / PO

- No controlled studies
- Only Retrospective Reports, case reports
- Childhood-onset dystonias, especially CP / Dystonia
- Effective oral doses range from 30–120 mg daily divided across 3–4 doses.
- Sedation, nausea, impaired mentation, dizziness
- Withdrawal reactions that include **delirium and seizures**.

Baclofen / Intrathecal

- Intrathecally via chronically implanted minipumps

- Only for CP / Dystonia with lower limb spasticity



Neurol Clin. 2015 February ; 33(1): 77–100

Benzodiazepines

- Alprazolam, chlordiazepoxide, ***clonazepam,*** and diazepam
- No large double-blind and controlled studies

- Suppressing phasic aspects of dystonia *(tremor, myoclonus, etc)*
- **Clonazepam;** especially in patients with blepharospasm and with myoclonic dystonia

(Starting 0.25 mg/day night dose; 0.25 mg/day increase every 3 day, max.dose 4 mg/day)

- sedation, impaired mentation and coordination, and depression
- **Addiction**

Dopaminergics for dystonia

- **Levodopa for DRD**

- Levodopa for myoclonus–dystonia, and rapid-onset dystonia–parkinsonism (RDP), etc:

Insufficient Response

Mov Disord. 2009;24(14):2163–4.

Anti- Dopaminergics for dystonia

Antipsycotics; old or new generation

Lang AE. Dopamine agonists and antagonists in the treatment of idiopathic dystonia. Adv Neurol. 1988;50:561

Marsden CD, Marion MH, Quinn N. The treatment of severe dystonia in children and adults. J Neurol Neurosurg Psychiatry1984;47(11):1166–73.

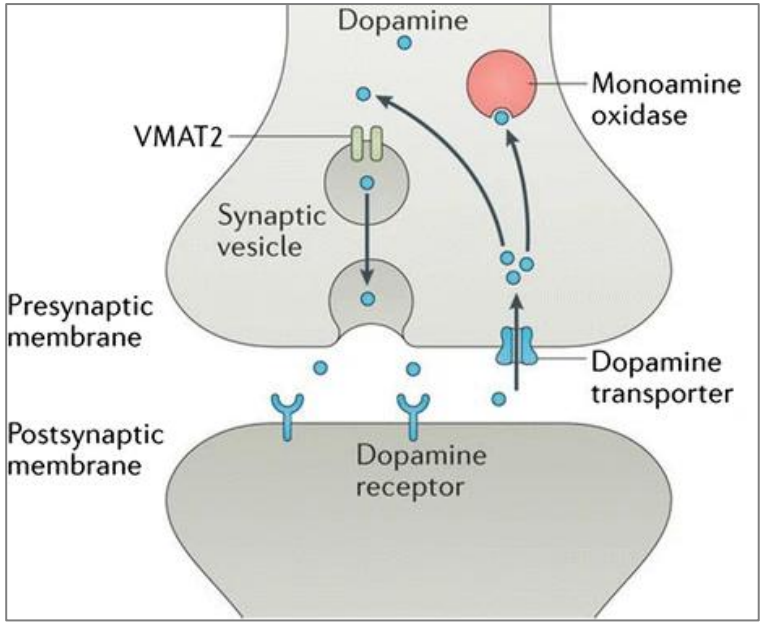
Girotti F, Scigliano G, Nardocci N, et al. Idiopathic dystonia neuropharmacological study. J Neurol. 1982;227(4):239–47

- Nonetheless controversial and currently discouraged because of their uncertain efficacy
- Severe side effects (Tardive syndrome)

Vesicular Monoamine Transporter-2 (VMAT2) inhibitors for dystonia

Depletion of neuroactive peptides such as dopamine in nerve terminals

Block vesicular storage of dopamine



Drugs (2018) 78:525–541

Vesicular Monoamine Transporter-2 (VMAT2) inhibitors for dystonia

	Deutetrabenazine	Tetrabenazine	Valbenazine
Dosage	6 mg, 9 mg, 12 mg	12.5 mg, 25 mg	40 mg, 60 mg, 80mg
Administration	Administer with food.	May administer without regard to meals	Administer with or without food
Indication	Chorea associated with Huntington disease, **Tardive dyskinesia**	Chorea associated with Huntington disease **Tardive dyskinesia**	**Tardive dyskinesia**
Contraindications	• Suicidal/untreated depression, • Hepatic impairment • Taking reserpine • Taking MAOI	• Suicidal/untreated depression • Hepatic impairment • Taking reserpine • Taking MAOI	• Hypersensitivity to valbenazine

Tardive dyskinesia / Dystonia

Adapted Life Style

Adult Onset (> 20 years)