

# Recent advances in the medical and surgical treatment of childhood movement disorders

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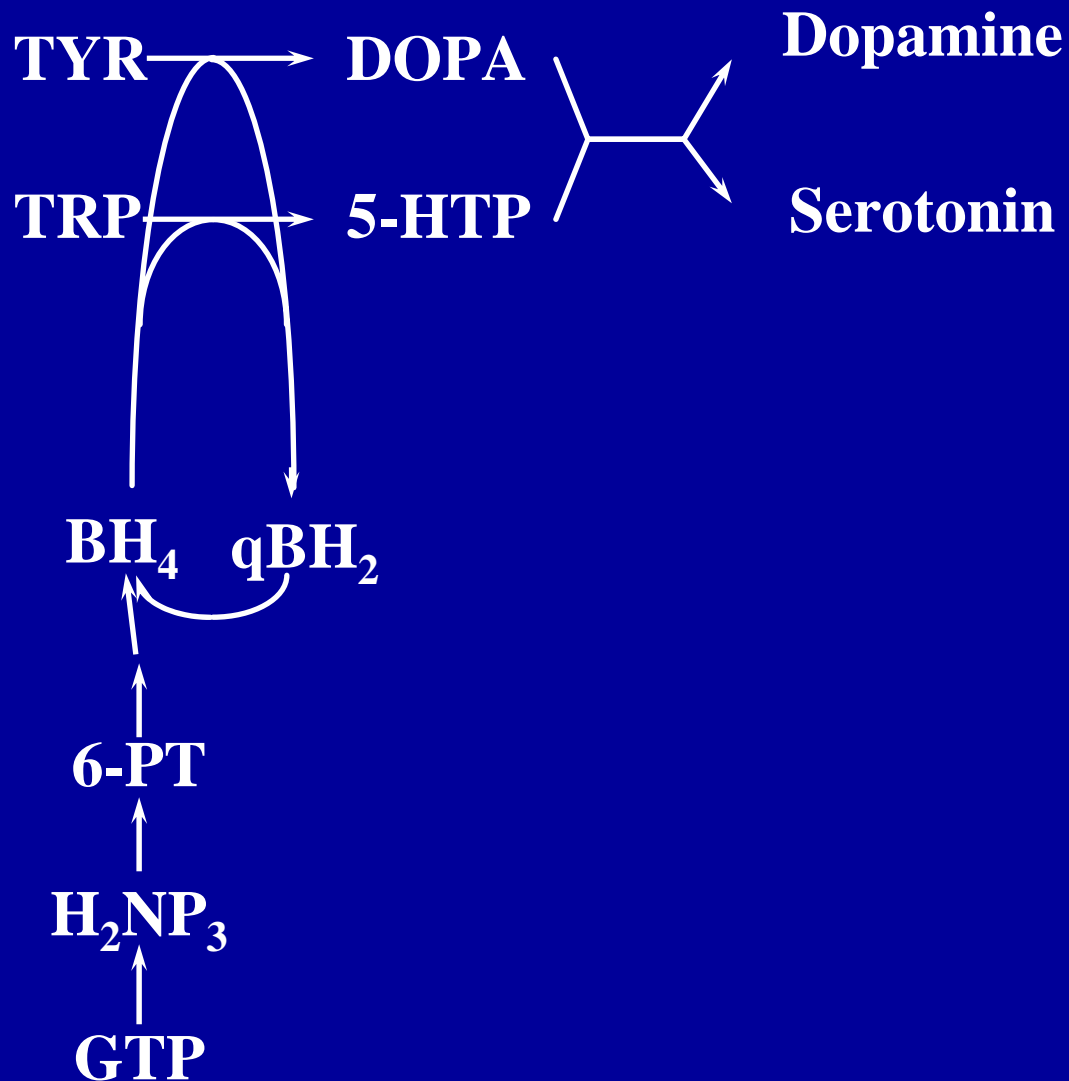
Institute of Child Health  
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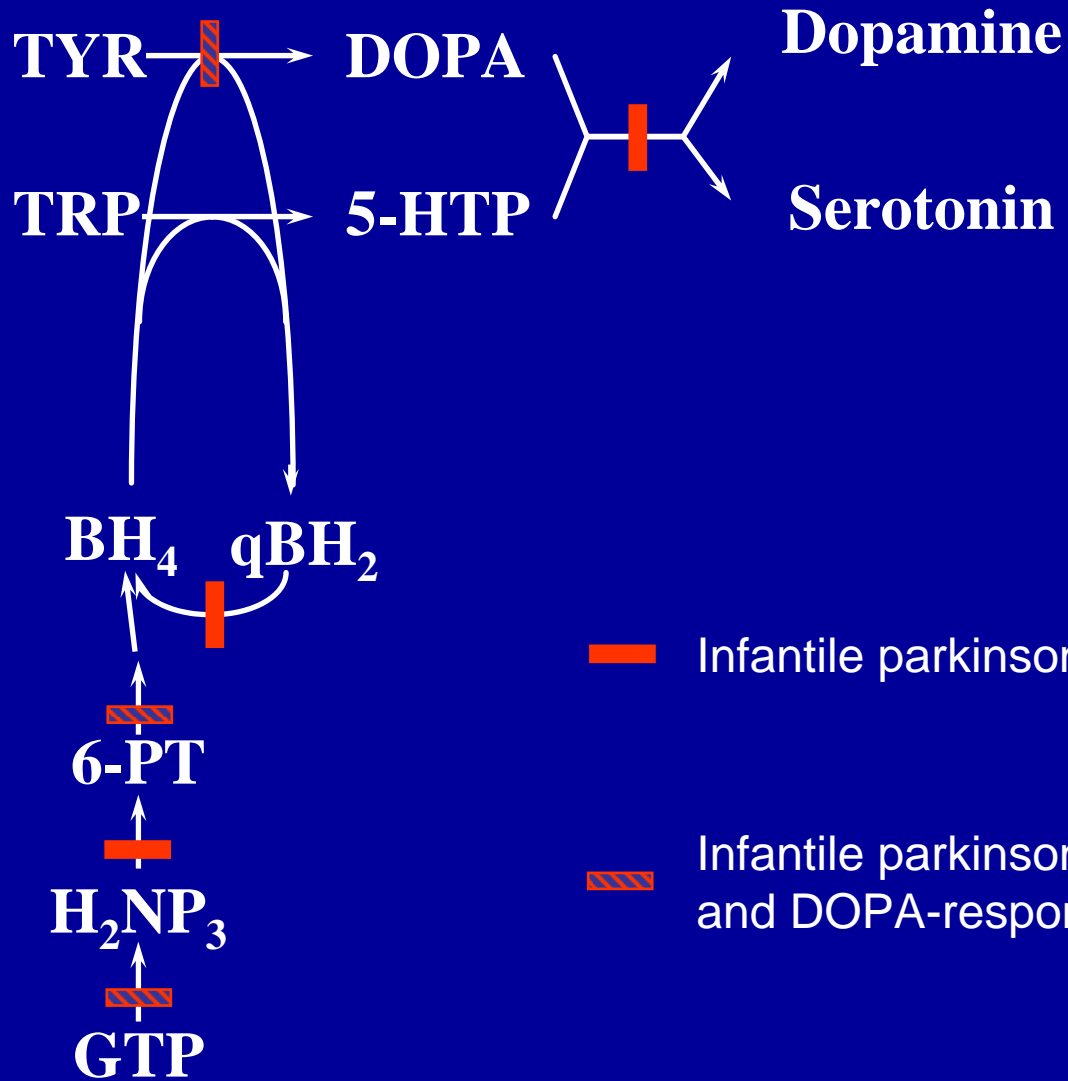
# Treatment of childhood MDs

- Specific
  - Some disorders of biogenic monoamine metabolism
  - Some paroxysmal dyskinesias
  - Sandifer syndrome
- Symptomatic
  - Dystonia
  - Chorea
  - Tics
  - Tremor
  - Myoclonus

Specific treatment

# Disorders of biogenic monoamine metabolism



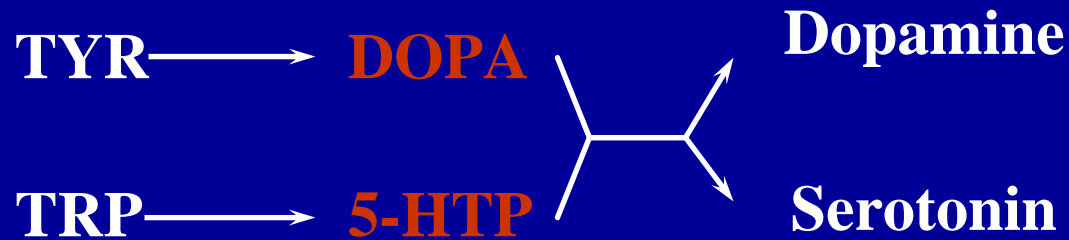


# Infantile parkinsonism-dystonia

- Dopamine deficiency alone
  - Tyrosine hydroxylase deficiency
- Dopamine and serotonin deficiency
  - Aromatic L-amino acid decarboxylase d.
- Dopamine, serotonin and tetrahydrobiopterin deficiency
  - GTP cyclohydrolase 1 deficiency
  - 6-pyruvoyltetrahydropterin synthase d.
  - Sepiapterin reductase deficiency

# Principles of neurotransmitter replacement therapy

- Must cross the blood-brain barrier
- Must interact with correct receptors



- Transported across BBB
- Precursors of neurotransmitter amines
- Always administered with a peripheral amine decarboxylase inhibitor (e.g. carbidopa)

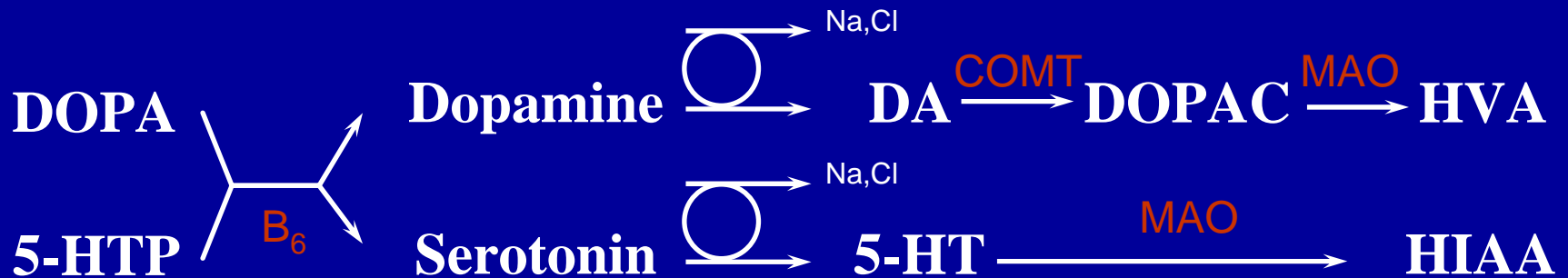
# Treatment of infantile parkinsonism-dystonia

- Dopamine deficiency
  - Laevodopa plus carbidopa
  - 1 to 10 mg/kg/day L-DOPA (4 to 6 doses)
- Serotonin deficiency
  - 5-hydroxytryptophan
  - 1 to 8 mg/kg/day (4 to 6 doses)
- Tetrahydrobiopterin deficiency
  - Tetrahydrobiopterin 2 to 10 mg/kg/day
  - Doesn't cross BBB well and given for other reasons

# Two problems

- Approach will not work for AAADC def.
  - Enzyme converts L-DOPA & 5HTP to DA and 5-HT
- Proportion of children with tyrosine hydroxylase deficiency do not respond to L-DOPA
  - Reasons unknown

# Possible solutions



- Give cofactor pyridoxal phosphate
- Inhibit reuptake
- Inhibit catechol-O-methyltransferase
- Inhibit monoamine oxidases
  - B for dopamine
  - A & B for serotonin

# DOPA-responsive dystonia

- Whatever the biochemical cause, only dopamine synthesis affected
- Segawa disease has a complete and sustained response to laevodopa
  - Low doses around 3 mg/kg/day
- Less typical forms may have variable laevodopa responsiveness
  - Doses up to 10 mg/kg/day
  - Inhibit MAO-B
  - Other anti-dystonic drugs

# Monoamine oxidase B inhibitor

## Selegiline

- 0.2 mg/kg/day morning and lunchtime
- Reduce dose L-DOPA by two thirds
- Main side effects
  - Dry mouth
  - Nausea
  - Insomnia

# Paroxysmal dyskinesias

- In childhood, most are secondary
- Primary paroxysmal dyskinesias
  - Paroxysmal kinesogenic choreoathetosis
  - Paroxysmal nonkinesogenic dystonia
  - Paroxysmal exercise-induced dystonia
  - Paroxysmal eating-induced dystonic choreoathetosis

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# Primary paroxysmal dyskinesias

- Likely all to be ion channel disorders
- May respond to ion channel blockers
  - Carbamazepine
  - Other AEDs
- May respond to altered pH
  - Acetazolamide
- PKC almost always responds to CBZ
- PEID is not treatable

# Sandifer syndrome



# Sandifer syndrome

- Caused by gastroesophageal reflux
- May respond to antireflux therapy
  - Omeprazole
- Cured by fundoplication

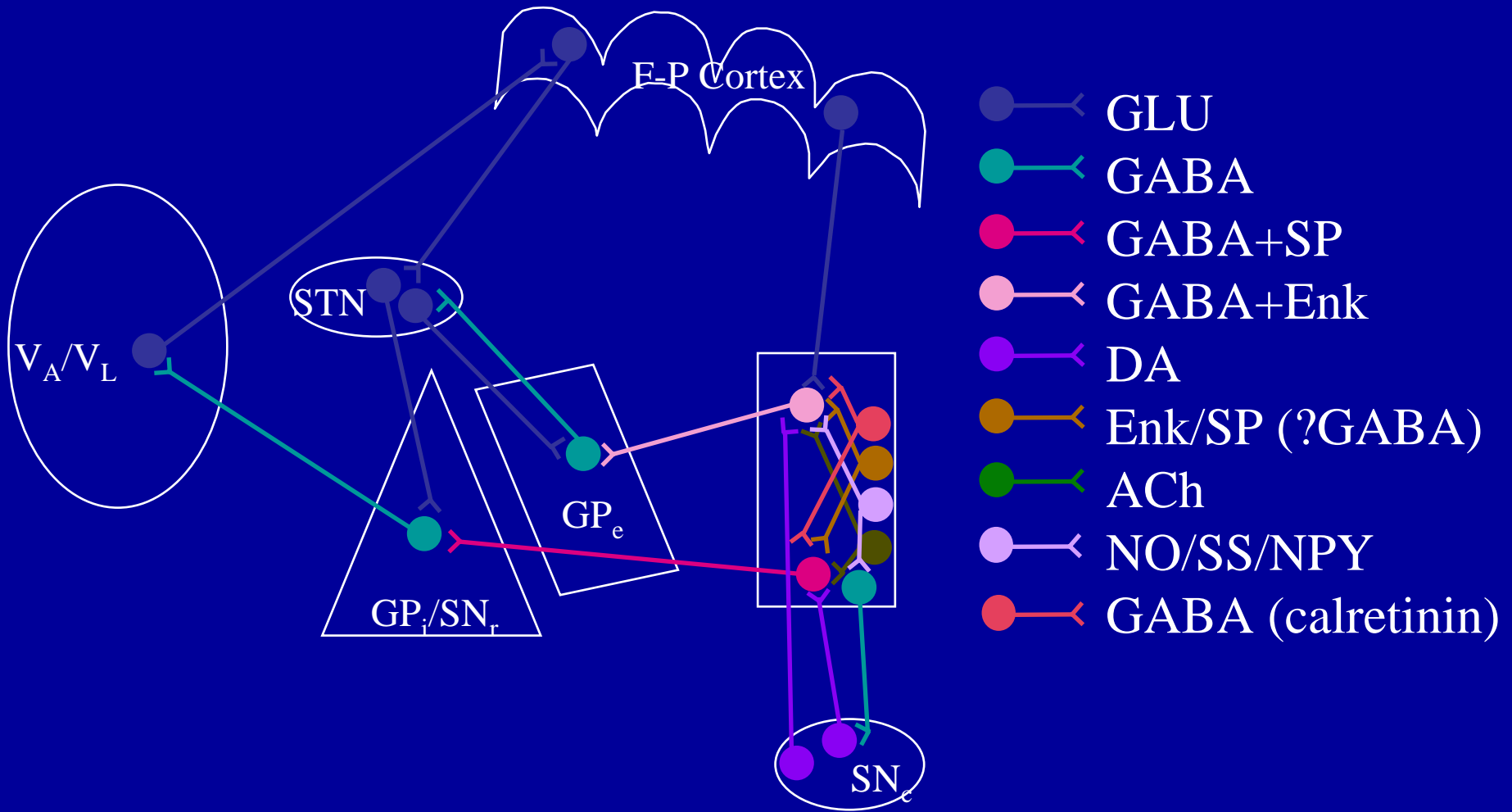
Symptomatic treatment

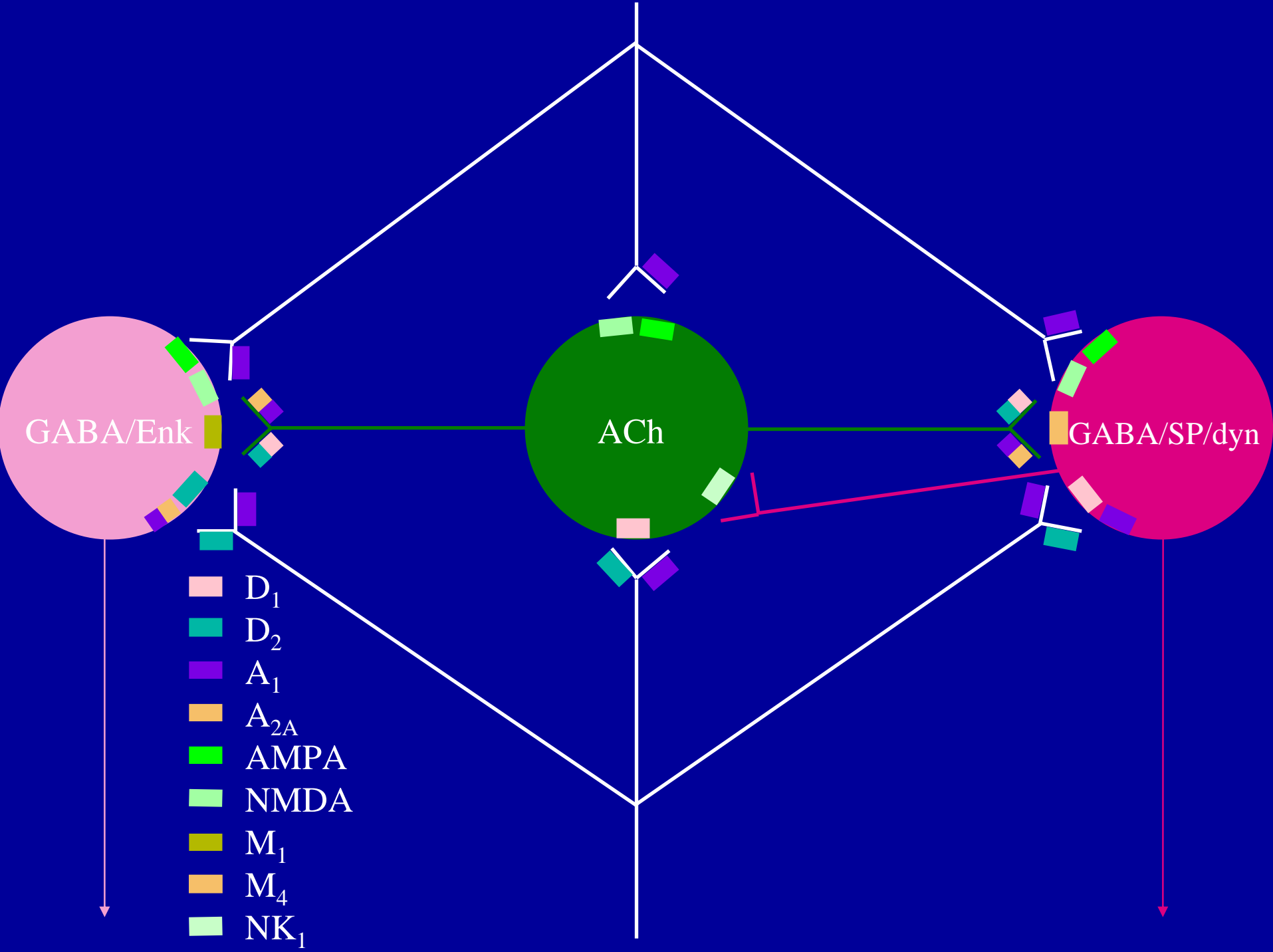
# Treatment of dystonia

- Anti-dystonia drugs
- Muscle relaxant drugs
- Botulinum toxin
- Deep brain stimulation
  
- Physical and occupational therapy
- Psychology
- Psychiatry

# Anti-dystonia drugs

- Levodopa plus carbidopa
- Antimuscarinic e.g. trihexyphenidyl
- Dopamine depletor e.g. tetrabenazine
- Dopamine blocker e.g. haloperidol
- Benzodiazepine e.g. clonazepam
- Anti-epileptic e.g. carbamazepine
- Haloperidol + tetrabenazine + trihexyphenidyl





# Laevodopa/carbidopa

- All children with dystonia should have a trial of laevodopa/carbidopa
- Start at 1 mg/kg/day L-DOPA in 4 doses and increase at weekly intervals until:
  - It is effective
  - Side effects occur
  - Total daily dose of 10 mg/kg/day

# Laevodopa/carbidopa

- Main side effects at higher doses
  - Nausea and vomiting
    - Give domperidone with each dose
  - Insomnia
    - Change dosing schedule
  - Chorea
- Continue maximally tolerated dose for at least 3 months before deciding ineffective

# Trihexyphenidyl

- Drug most likely to have a favourable effect
- Start at 0.5 mg (infant), 1 mg (child) or 2 mg (adolescent) three times a day
- Increase by 0.5, 1 or 2mg per day each week until:
  - It is effective
  - Side effects occur
  - Total daily dose of 9, 30 or 90 mg is reached

# Trihexyphenidyl

- Main side effects (n.b. pupil dilatation shows it is having an antimuscarinic effect)
  - Dry eyes and mouth
  - Gastrointestinal disturbance
  - Urinary retention
  - Behavioural disturbance
- May need very high doses to be effective

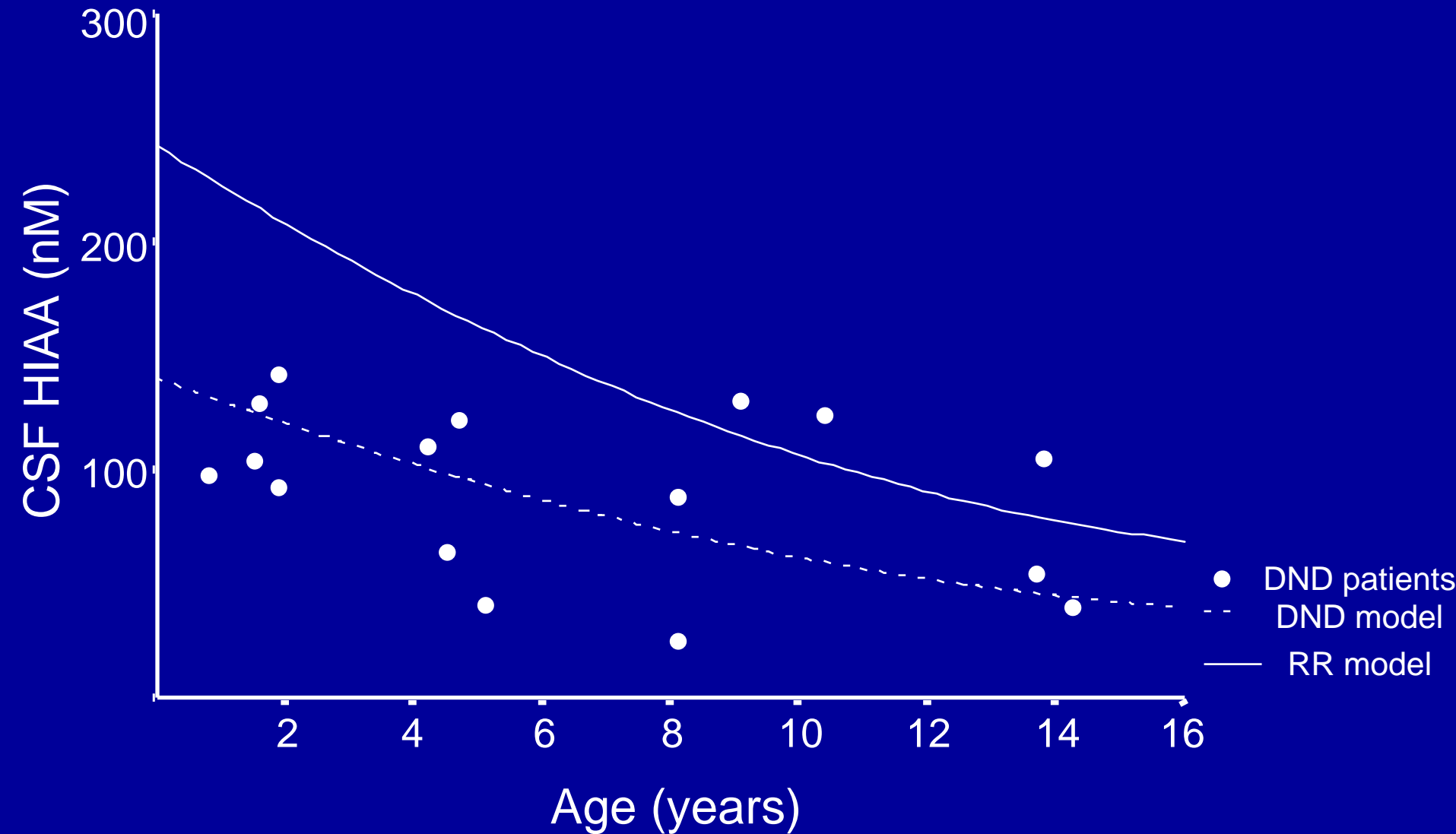
# Tetrabenazine

- Probably the next most effective drug
- Start at 1 mg/kg/day in three doses
- Increase at weekly intervals up to 4 mg/kg/day
- Stop if no improvement after 1 week on maximum dose
- Main side effects
  - Drowsiness
  - Depression
  - Behavioural change

# Triple therapy for dystonia

- Principle
  - Induce parkinsonism with combination of a dopamine depletor and a dopamine blocker
  - Treat parkinsonian tremor with an anti-muscarinic
- Practise
  - Start tetrabenazine at 1 mg/kg/day
  - Add haloperidol at 0.025 mg/kg/day in two doses, increase by 0.025 mg/kg at weekly intervals until parkinsonism induced
  - Add trihexyphenidyl

# A role for serotonin?



- Reduced CNS serotonin turnover in children with DOPA-nonresponsive dystonia
- Serotonin turnover can be increased with
  - Pyridoxine or pyridoxal phosphate
  - 5-hydroxytryptophan
  - Selective serotonin re-uptake inhibitors
- A trial is needed

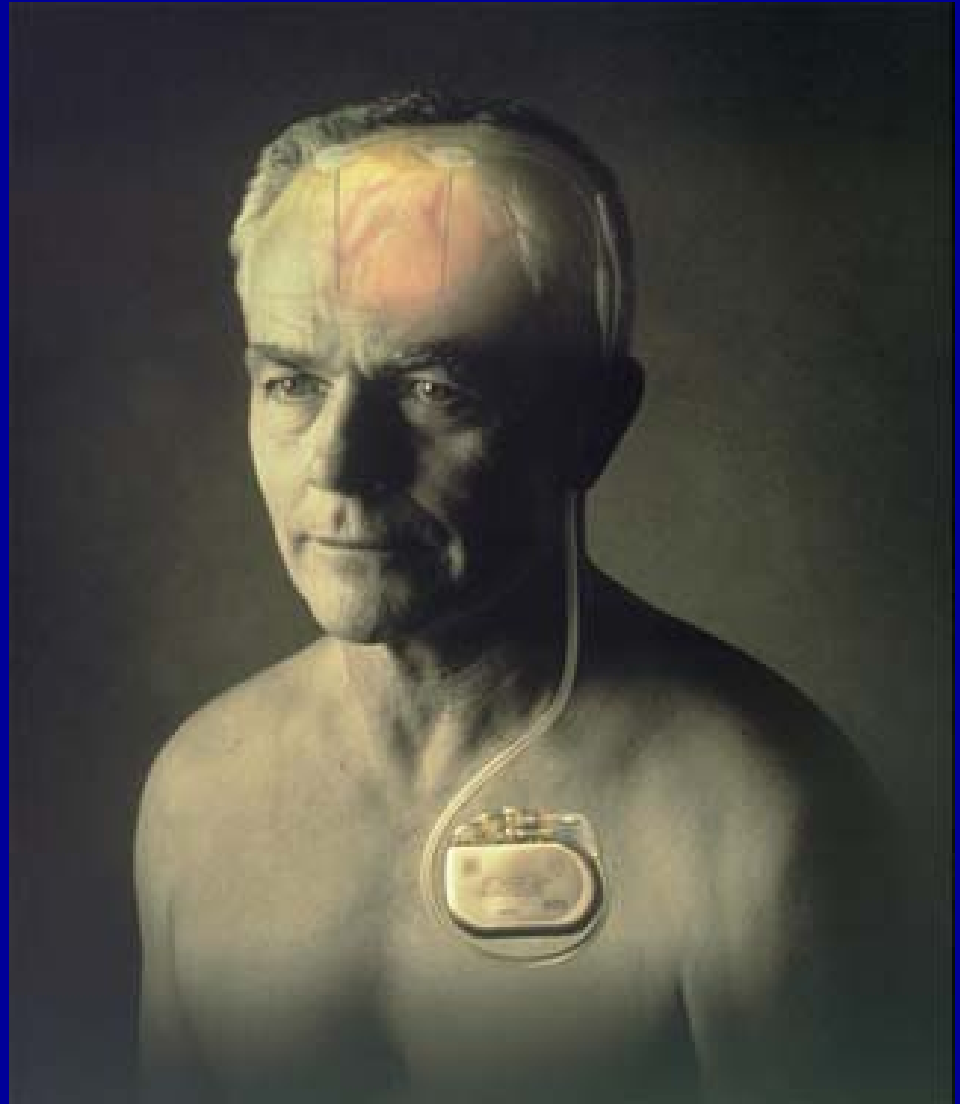
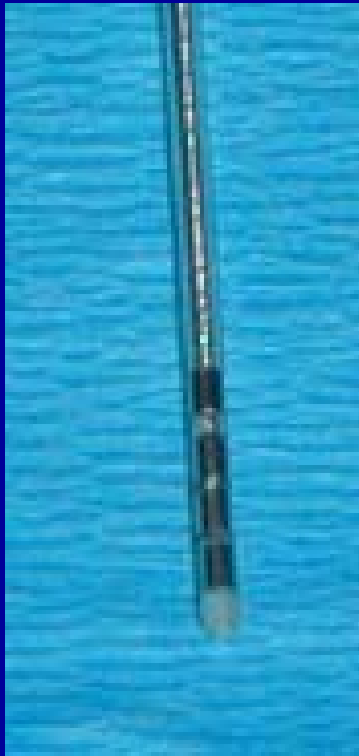
# Botulinum toxin

- Treatment of choice for focal dystonia (which is very rare in childhood)
- In generalized dystonia is used
  - To treat focal fixed dystonia
  - To treat painful dystonia

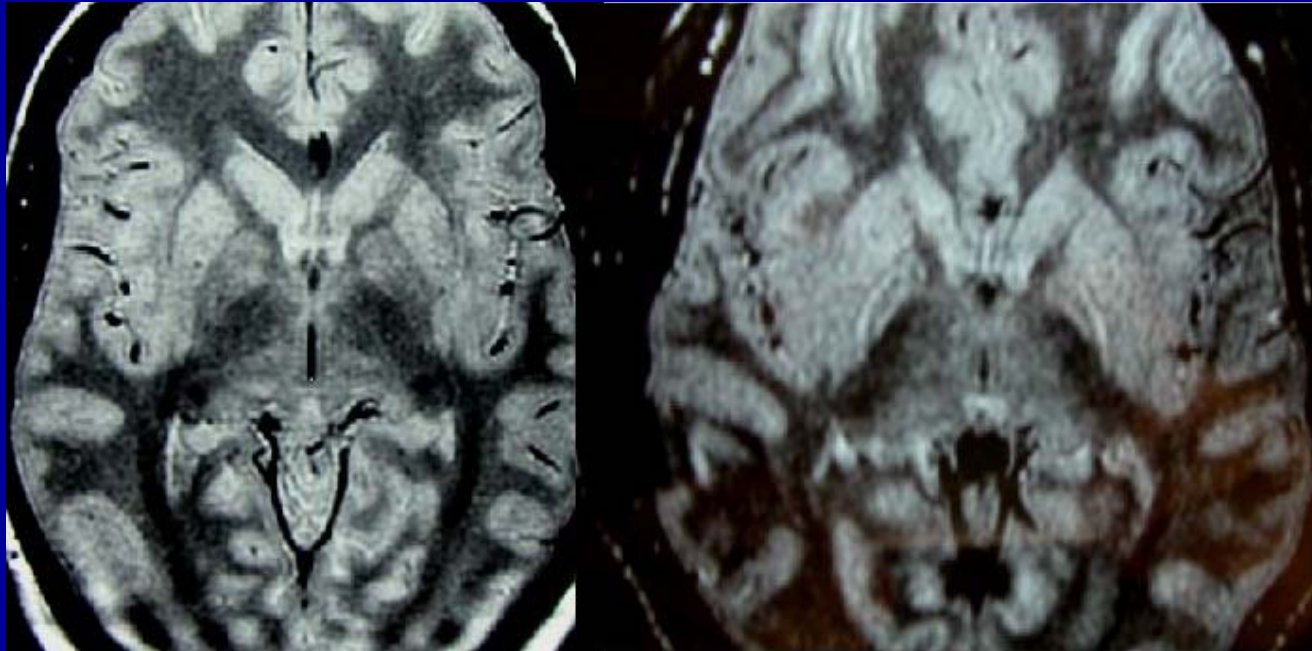
# Deep brain stimulation

- Bilateral pallidal stimulation
  - Effective in adults with young onset idiopathic generalized dystonia
    - Cross over trial
    - Case series
  - Reduces severity of dystonia and number anti-dystonia drugs
  - Effective in children with primary and secondary dystonia
    - Case reports and small series

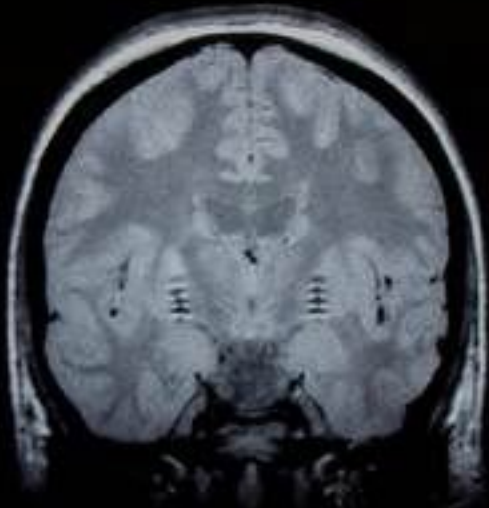
# Surgical technique



# Surgical technique



- Direct targeting of posteroventral globus pallidus interna from stereotactic proton density MRI



# Status dystonicus

- Severe, continuous dystonic spasms
- Medical emergency
- Rhabdomyolysis
  - Monitor blood sugar, amylase and renal function
- Respiratory compromise
- Exhaustion

# Status dystonicus

- Initial management
  - Treat any triggering factors
  - Heavy sedation
    - Dystonia ameliorates when asleep
    - Combination benzodiazepines and chloral
    - Intravenous chlormethiazole (if available)
- Anti-dystonia therapy
  - Intravenous anti-muscarinic (titrate to pupil size)
    - Benztropine 2 mg twice daily
  - Haloperidol 0.05 mg/kg/day

# Generalized dystonia

- Chronic, progressive motor disability
- Cognitive abilities intact
- Communication difficult
- Starts mid-childhood to adolescence
- Difficult to treat effectively

# Generalized dystonia

- Physical therapy
- Occupational therapy
- Communication aids
- Appropriate education
- Psychosocial intervention
- Psychiatry

# Conclusions

- There have been recent advances in both medical and surgical treatments for dystonia
- Resulting from a better understanding of pathogenesis
- No trials of treatment in children
- Deep brain stimulation is very promising