Diagnosis and Treatment of Tardive Syndrome

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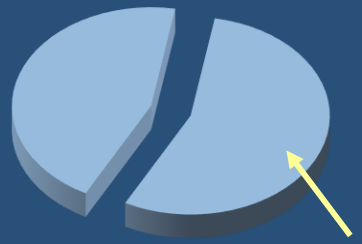
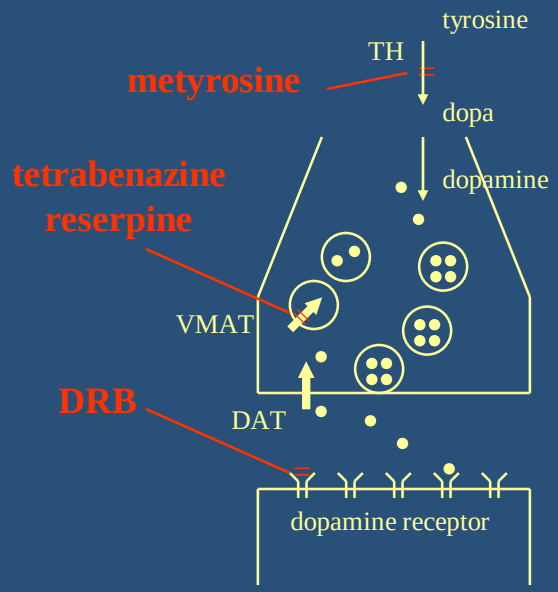
Drug-Induced Movement Disorders



movement disorders caused by anti-dopaminergics
aka. extrapyramidal syndrome (EPS)

EPS
- acute/subacute: dystonia, akathisia, neuroleptic malignant syndrome
- dose-dependent: parkinsonism, drug-induced tremor
- delayed: tardive syndrome

Anti-Dopaminergic Drugs



Dopamine Depletors (DD): presynaptic
metyrosine – tyrosine hydroxylase
reserpine – VMAT 1&2 (vesicular monoamine transporter)
benazines – VMAT 2

Dopamine Receptor Blockers (DRB): postsynaptic
typical neuroleptics
atypical neuroleptics
anti-emetics

DD & DRB → acute/subacute EPS
dose-dependent EPS
DRB → tardive syndrome

Tardive Syndrome

onset when on anti-dopaminergic: > 1 month of exposure

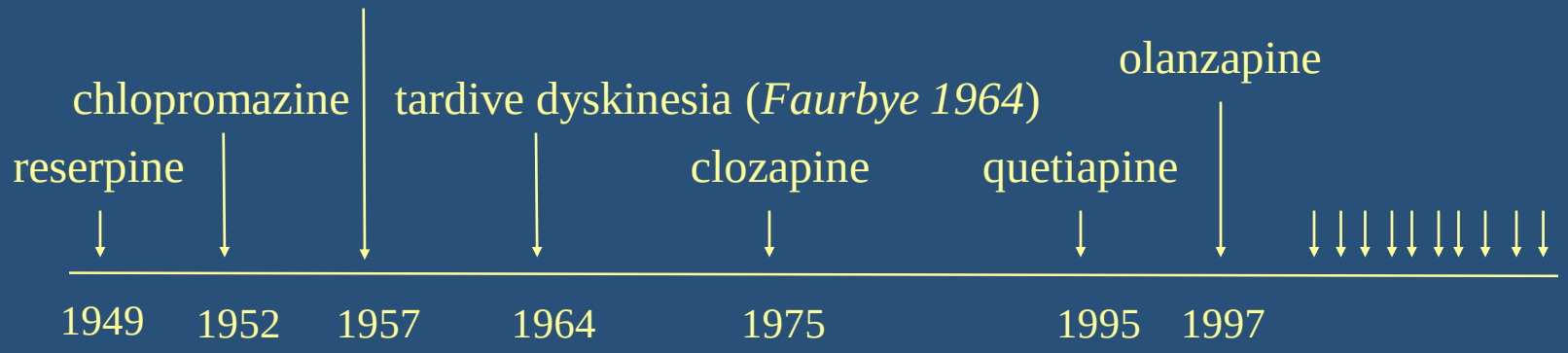
onset when off anti-dopaminergic: "unmasked" phenomenon
- mostly within 6 months
- occasionally 6-12 months
- never > 12 months

- idiosyncratic: no safe threshold, risk ↑ as duration ↑
- prevalence ≈ 5-20 %
- risk factors
  - duration
  - typical > atypical neuroleptics
  - dosage
  - female > male
  - older > younger
  - drug holidays & interruptions

- natural history: non-progressive, spontaneous remission possible

History of Tardive Syndrome

paroxysmal dyskinesia as the effect of Megaphen (*Schönecker 1957*)



Dopamine Receptor Blockers: typical *vs* atypical neuroleptics

risk of EPS ≃ binding affinity to D2 receptor

	D1	D2	D3	D4	D5
region	striatum	striatum	accumbens	frontal	hippocampus

	haloperidol	clozapine	quetiapine	olanzapine	risperidone
D1	15	53	390	10	21
D2	**0.82**	**360**	**39**	**2.1**	**0.44**
D3	2.5	22	>500	17	13
5HT1A	2600	710	>830	7100	21
M1	570	0.98	56	2.1	>5000

“atypicalness”: clozapine >>> quetiapine >> olanzapine > risperidone

Dopamine Receptor Blockers: newer neuroleptics

	EPS	metabolic syndrome (weight gain, diabetes,etc)	QTc prolongation
clozapine	+/-	++++	+
quetiapine	+	+++	+
olanzapine	+	++++	+
aripiprazole (Abilify)	+	+	+/-
ziprasidone (Geodon)	+	+/-	++
iloperidone (Fanapt)	+	++	++
lurasidone (Latuda)	++	+/-	+/-
asenapine (Saphris)	+++	++	+
paliperidone (Invega)	+++	+++	+
cariprazine (Vraylar)	++	++	-

Pimavanserin (Nuplazid): a novel antipsychotic

- approved in 2016 for Parkinson disease with psychosis
- inverse agonist of serotonin 5-HT_{2A} receptor
- no appreciable affinity to dopaminergic D2 receptor (Ki >300 nM)

Table 1 **Adverse Reactions in Placebo-Controlled Studies of 6-Week Treatment Duration and Reported in ≥2% and >Placebo**

Percentage of Patients Reporting Adverse Reaction		
	NUPLAZID 34 mg	**Placebo**
	N=202	N=231
Gastrointestinal disorders		
Nausea	7%	4%
Constipation	4%	3%
General disorders		
Peripheral edema	7%	2%
Gait disturbance	2%	<1%
Psychiatric disorders		
Hallucination[a]	5%	3%
Confusional state	6%	3%

Dopamine Receptor Blockers: central *vs* peripheral anti-emetics

	prochlorperazine (Compazine) metoclopramide (Reglan) promathazine (Phenergan)	trimethobenzamide (Tigan) domperidone (Motilium)
blood-brain barrier	+	–
risk of EPS	+	–

Tardive Syndrome

- classic tardive dyskinesia
- tardive dystonia
- tardive akathisia
- tardive pain (focal akathisia)
- tardive chorea (withdrawal emergent syndrome)
- tardive myoclonus?
  - tremor?
  - tics?
  - parkinsonism??

tardive dyskinesia in a broader sense = tardive syndrome
tardive dyskinesia in a narrower sense → one of many types of tardive syndrome

Classic Tardive Dyskinesia

- repetitive, stereotyped and rhythmic- tardive stereotypy

  face, mouth, tongue: oral-buccal-lingual dyskinesia (OBLD)
  “flycatcher’s tongue “
  limbs: distal > proximal
  “piano-playing fingers”
  abdominal and pelvic dyskinesia
  vocal dyskinesia

- absent during voluntary movements
- psychosocial impact >>> physical impact

Tardive Dystonia

- proximal > distal

  - mouth – oromandibular dystonia (OMD)
  - axial – retrocollis, opistotonus, rotation of shoulders & extension of elbows

- most common cause of secondary dystonia

- phenomenologically indistinguishable from idiopathic dystonia

Tardive Akathisia

- subjective restless feeling & objective restless movements
- phenomenologically indistinguishable from akathisia of acute EPS
- focal tardive akathisia(tardive pain): oral or pelvic

Diagnosis

1. history of exposure to DRB
2. phenomenology of movements consistent with tardive syndrome
3. excluding other etiologies

"double dyskinesia": an underlying hyperkinetic movement disorder + tardive syndrome

"pseudo-tardive dyskinesia": consistent phenomenology, but caused by other etiologies

Treatment – continue DRBs or not

- spontaneous remission after discontinuation of DRBs
  - 33 % in classic tardive dyskinesia
  - 12 % in tardive dystonia
  - 8 % in tardive akathisia (*Burke* 1989)

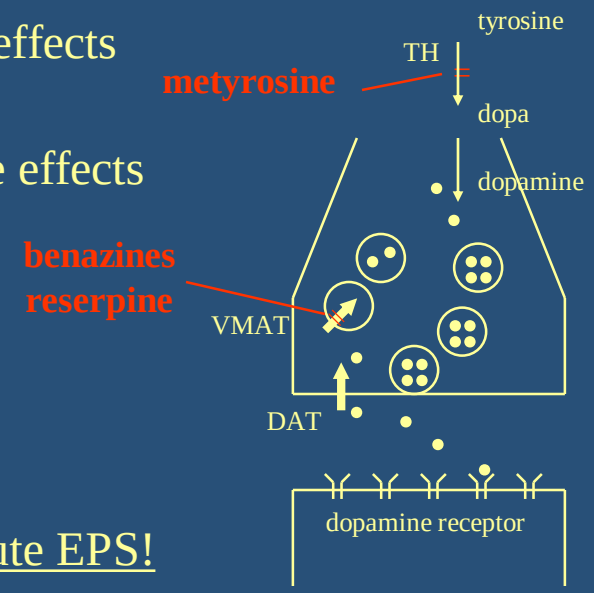
- does continuing DRBs worsen tardive syndrome?
  - symptoms – No (*Casey* 1986, *Gardos* 1988)
  - natural course – ? (*Kang* 1986)

- does symptomatic treatment of tardive syndrome change its natural course?
  - ???

Treatment – classic tardive dyskinesia

- to treat or not to treat
- dopamine depletors (tetrabenazine > reserpine > metyrosine)

benazines – reversible VMAT2 inhibitor
short half-life & less peripheral adverse effects
reserpine – irreversible VMAT1&2 inhibitor
long half-life & more peripheral adverse effects
metyrosine – low potency



- GABAergics (benzodiazepines, vaproate, baclofen)

- may be worsened by anticholinergics- different from acute EPS!

VMAT2 Inhibitors- benazines

	approval date	approved indication	risk of depression	dosing
tetrabenazine (Xenazine)	2008	Huntington chorea	+++ (19%)	bid-tid
deutetrabenazine (Austedo)	2017	Huntington chorea tardive dyskinesia	+ (2-4%)	bid
valbenazine (Ingrezza)	2017	tardive dyskinesia	- (< 1%)	qd

Treatment – tardive dystonia

anticholinergic responders

dopamine-depletor responders

- baclofen
- botulinum toxin injection
- deep brain stimulation of globus pallidus internus (GPi DBS)

Treatment – tardive akathisia

- not responsive to anticholinergics- different from acute EPS

- responsive to dopamine depletors: benazines
- gabapentin
- clonidine
- opioids
- amantadine

Mechanism of Tardive Syndrome

- mechanism – denervation hypersensitivity
- pathology – no obvious morphological changes
  subtle biochemical abnormalities
  (*Christensen* 1970, *Jellinger* 1977, *Harrison* 1999)

- genetics – dopamine D2 or D3 receptors polymorphism
  (*Steen* 1997, *Segman* 1999, *Kishida* 2004)

- animal models
  rodents – acute EPS but no tardive syndrome
  primates – tardive syndrome
  no obvious morphological changes
  subtle biochemical changes
  (*Gunne* 1984, *Mitchell* 1992, *Eyles* 2000, *Klintenberg* 2002)

- functional imaging – no changes in dopaminergic transmission
  (*Blin* 1989, *Lavalaye* 2001, *Adler* 2002)

Conclusions

- Think thrice before starting DRB and use safer ones if possible.
- Diagnosis of tardive syndrome is straightforward,
  but don’t forget about double or pseudo-tardive dyskinesia.
- Tailor treatment to the type of tardive syndrome.
- Always communicate with the physician who started DRB!