Neurological adverse effects of antipsychotic drugs and management

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ANTIPSYCHOTICS

Psychotropic drugs are those having primary effects on *Psyche* (mental processes) and are used for treatment Of Psychiatric disorders

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One of the primary psychotic disorders in which the Antipsychotics works is the,

Psychosis

Psychosis:

These are severe psychiatric Illness with serious distortion of thought, behavior, capacity to recognize reality and of perception (delusions and hallucinations).

Psychosis is a symptom not a diagnosis and should prompt a search for an etiology.

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Psychotic symptoms :

- Schizophrenia
- Mood disorder
- Dementia
- Delirium
- Medical causes
- Metabolic disorder
- Nutritional deficiencies
- Meningitis or encephalitis
- Intracranial bleeding
- Drug withdrawal, intoxication

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Antipsychotic drugs are also known as Neuroleptics, Major Tranquilizer and Anti-Schizophrenic drugs. A first generation of antipsychotics, known as Typical antipsychotics, was discovered in the 1950s. Most of the drugs in the second generation, known as Atypical antipsychotics, have been developed more recently.

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Classification:

A. **Typical Antipsychotics:**

1. **Phenothiazines:**

   a. **Aliphatic side chain:** Chlorpromazine, Triflupromazine

   b. **Piperidine side chain:** Thioridazine

   c. **Piperazine side chain:** Trifluoperazine, Fluphenazine

2. **Butyrophenones:** Haloperidol,

3. **Thioxanthenes:** Flupenthixol

4. **Other heterocyclics:** Pimozide,

B. **Atypical neuroleptics:** Clozapine, Risperidone, Olanzapine, Quetiapine, Aripiprazole, Ziprasidone.

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Mechanism of Action:

-Antipsychotic blocks D_2 receptors in the brain's Dopaminergic pathway.

-Some also block or partially block serotonin receptors (particularly $5HT_{1A, C}$ and $5HT_{1A}$ receptors)

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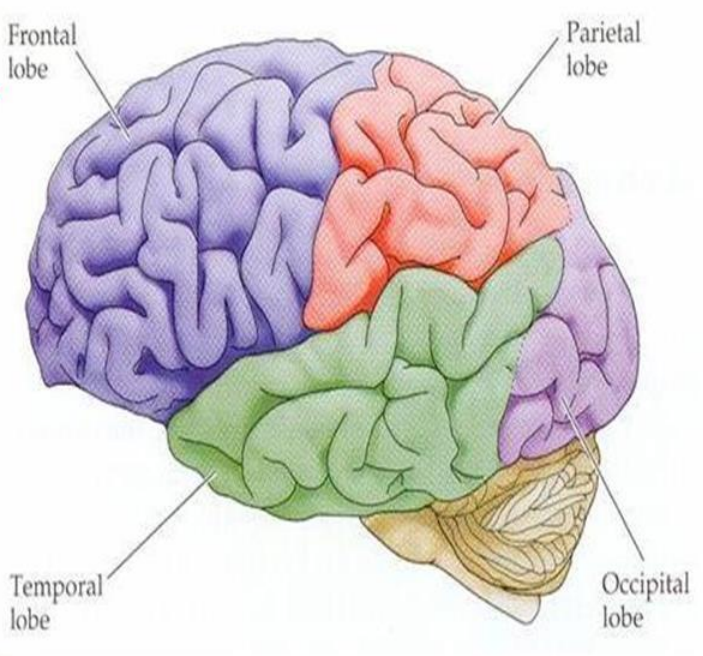
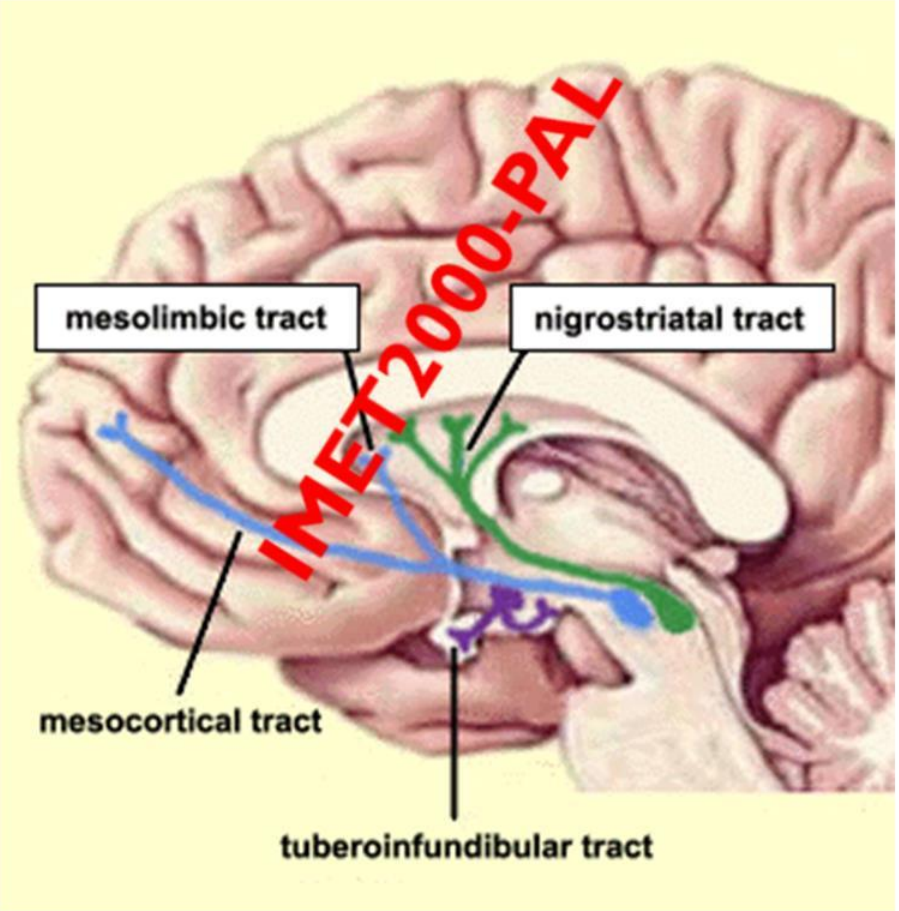


-But antipsychotic drugs can also block wide range of receptor targets.

Dopaminergic pathway in Brain:

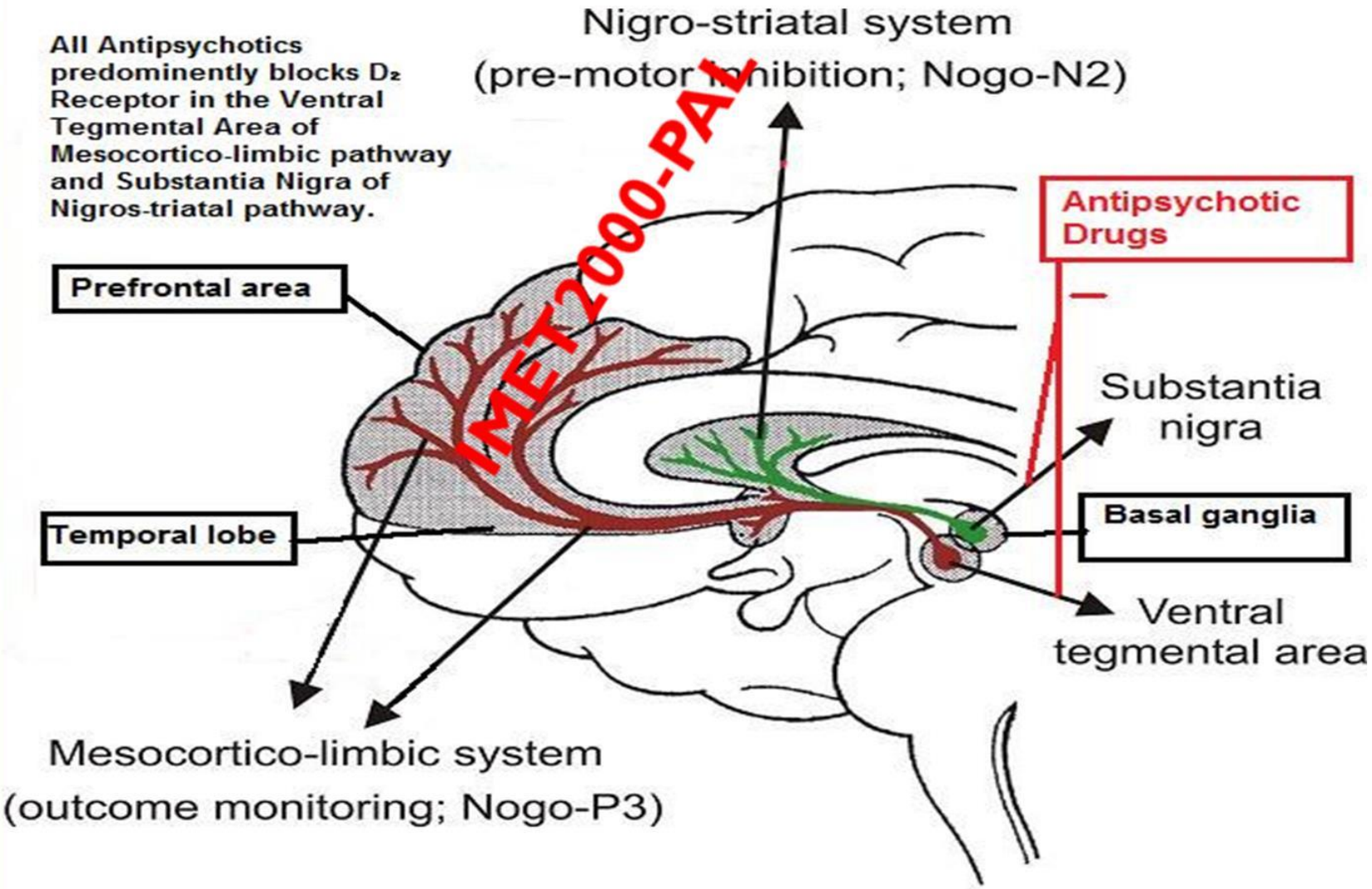


Mesolimbic- mesocortical: Control behavior, cognitive funtion regulated by D_2 Receptor.

Nigrostriatal: Control Voluntary Movement regulated by D_1 and D_2 receptor.

Tuberoinfundibular: Control prolactin secretion Regulated by D_2 receptor.

In the Mesolimbic- Mesocortical and Nigrostriatal pathway Antipsychotic blocks:



Atypical Antisychotic drugs

These are newer 2nd Generation antipsychotics that have weak D_2 receptor blocking but potent 5-HT_2 antagonistic activity. They May improve the impaired Cognitive function in psychotics.

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Atypical Antisychotic drugs

- ATYPICAL NEUROLEPTICS:
  - Risperidone (Risperdal ®)
  - Clozapine(Leponex ®)
  - Olanzapine (Zyprexa ®)
  - Quetiapine (Seroquel ®)
  - Ziprasidon (Geodon)
  - Lurasidon

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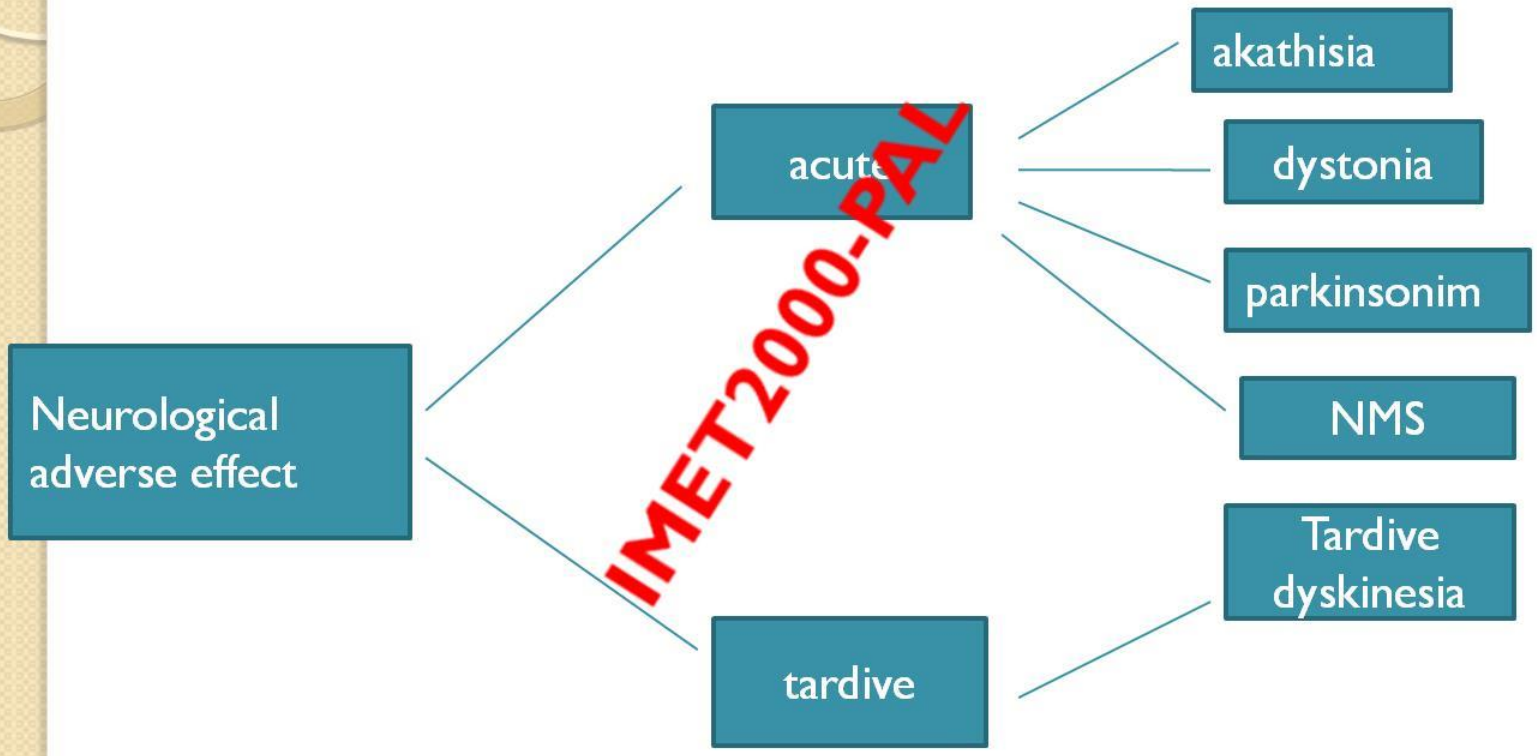
Neurological side effects



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Acute dystonia

- Is characterized by intermittent or sustained involuntary contraction or spasm of the muscles that result in twisting repetitive movement or abnormal posture , which develops within seven days of starting or rapidly raising the dose of antipsychotic or of reducing the medication used to treat acute EPS (antichlinergic agent)

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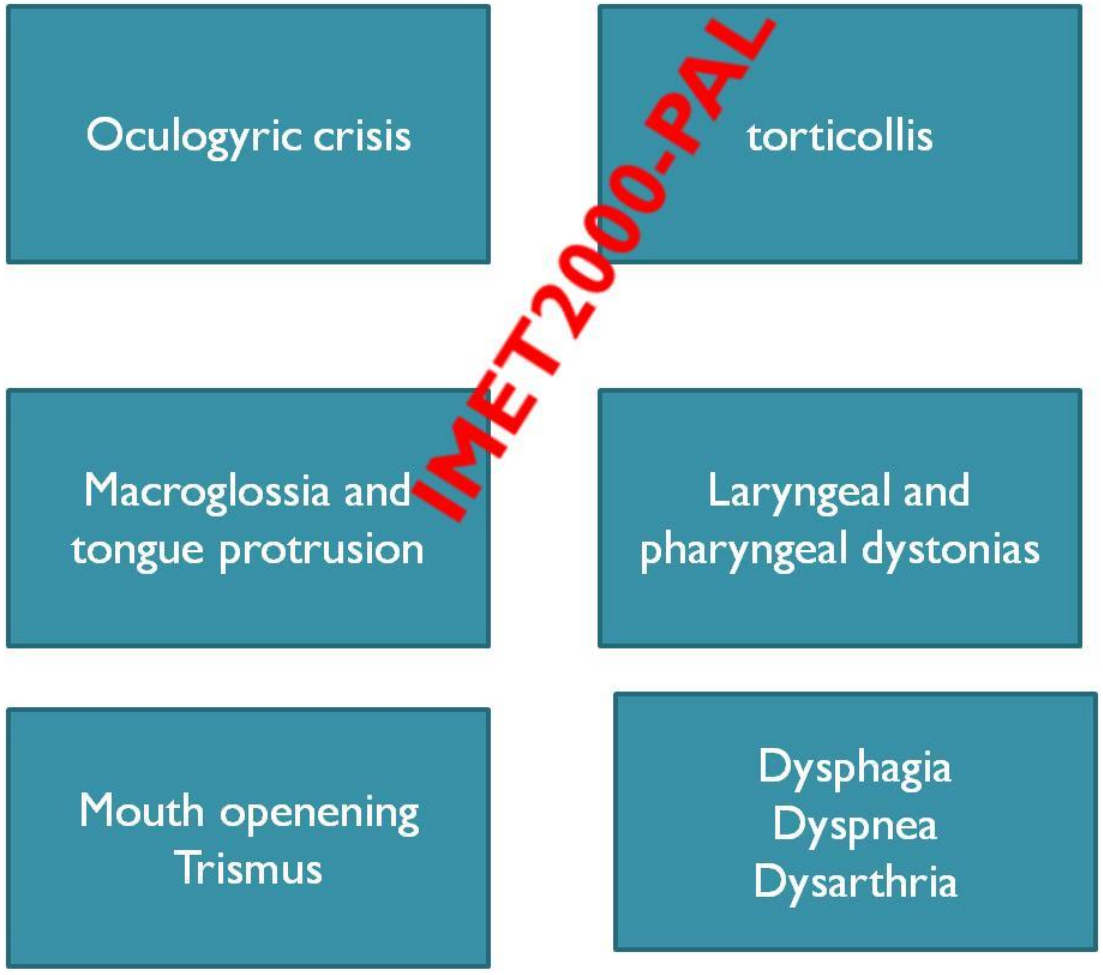
Types of dystonia



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Motor presentations of acute dystonia

- Torticollis , head held turned in one side .
- Oculogyric crisis , spasm of extra orbital muscles .
- Blepharospasm .
- Buccolingual crisis , dysarthria ,grimacing , mouth opening , dysphagia
- Macroglossia , tongue protrude , feels swallon.
- larengeal spasm with respiratory stridor , dyspnea .
- Opisthotonus , painful forced extension of neck when severe the back arches .
- Spasticity , trunk muscles and limbs can be affected .

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Examples of medication and differential diagnose

- Antipsychotics or antiemetics with dopamine blocking activity (haloperidole, metoclopromide) .
- Antihistaminic (promethazine)
- Antidepressant (SSRI)
- H2 antagonist , calcium channel blocker .
- differential diagnose , tetanus ,wilson disease , hypocalcaemia , hypomagnesia , conversion , malingering ,temporal epilepsy .
- Tardive dystonia occurs only after months or years , doesn't improve rapidly ,

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The treatment

- The recommended first choice is an injectable anticholinergics agent (benztropin , biperiden) or antihistamine with anticholinergics(promethazine 25-50 mgIM injection) or diazepam 5-10mg IV .
- Usually effective within 20 minutes , second injection after half an hour maybe needed .
- Oral anticholinergics should be continued for 24-48 hours to prevent occurrence 4-7 days .
- The precipitating antipsychotic should be avoided , another medicine from different class is recommended .

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Acute antipsychotic-induced akathisia

- It's **characterized** by strong feelings of inner restlessness that manifest as excessive walking or pacing and difficulty remaining still .
- A common problem is to distinguish from psychomotor agitation associated with psychosis .
- Akathisia is characterized by at least **five subtype** :

. **Acute** akathisia , begins hours or days after starting and last less than 3 months

. **Tardive** arise within 3-4 months of starting and persist for years .

. **Chronic** akathisia , last more than 3 months , no temporal correlation antipsychotic .

. **Withdrawal** akathisia , begins within 6 weeks of discontinuing or reducing the dosage .

. **Pseudo** akathisia , objective symptoms of movement without subjective distress .

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Drugs that can cause akathisia

- Antipsychotics including first and second generation , especially high potency FGA .
- Selective serotonin reuptake inhibitor (SSRI).
- Metoclopramide .
- Levodopa .
- Dopamine receptor agonist .

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DSM-IV-TR criteria for acute akathisia

- A. Subjective complaints of restlessness after exposure to antipsychotic .
- B. At least one of the following is observed :

  . Fidgety movement or swinging of the legs .

  . Rocking from foot to foot while standing .

  . Pacing .

  . Inability to sit or stand still for at least several minutes .
- C. symptoms develop within 4 weeks of starting or raising the dosage or after reducing a medication used to treat EPS .

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Akathisia and SGA drugs

- Low propensity to induce EPS .
- The CATIE study revealed no significant difference between FGA and four SGAs in the percentage of patient who developed acute akathisia (olanzapine 10% , quetiapine 13% , ziprasidon 28% and a remarkable high rate 15-25% in patients treated with aripiprazol (abilify drug) , clozapine has the lowest risk).

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Current treatment options for akathisia

- Two major strategy :

1. Modification of antipsychotic drug regime .
2. And or the addition of anti akathisia agent.

- The former includes a dose reduction, switch to a low potency FGA or to a more commonly used SGA (quetiapine) and by resistant (clozapine)
- **Beta blocker** (propranol) are most widely used , maximal dose 120 mg/day , monitor adverse effects , blood pressure ,pulse .
- But not supported by large scale control trial and tolerability was poor .
- **Benzodiazepine** (clonazepam ,lorazepam) non specific anti anxiety and sedative effect , clinical experience should choose that these effects are not sufficient to ameliorate akathisia .
- **Anticholinergics** , their effect unclear , only in patients who have associated parkinsonin symptom .
- Agents with marked 5-HT2a receptor antagonist (cyproheptadine)
- **Mirtazipine** , 5-HT2a antagonist , is a new class for effective ,can be given 15 mg one daily .

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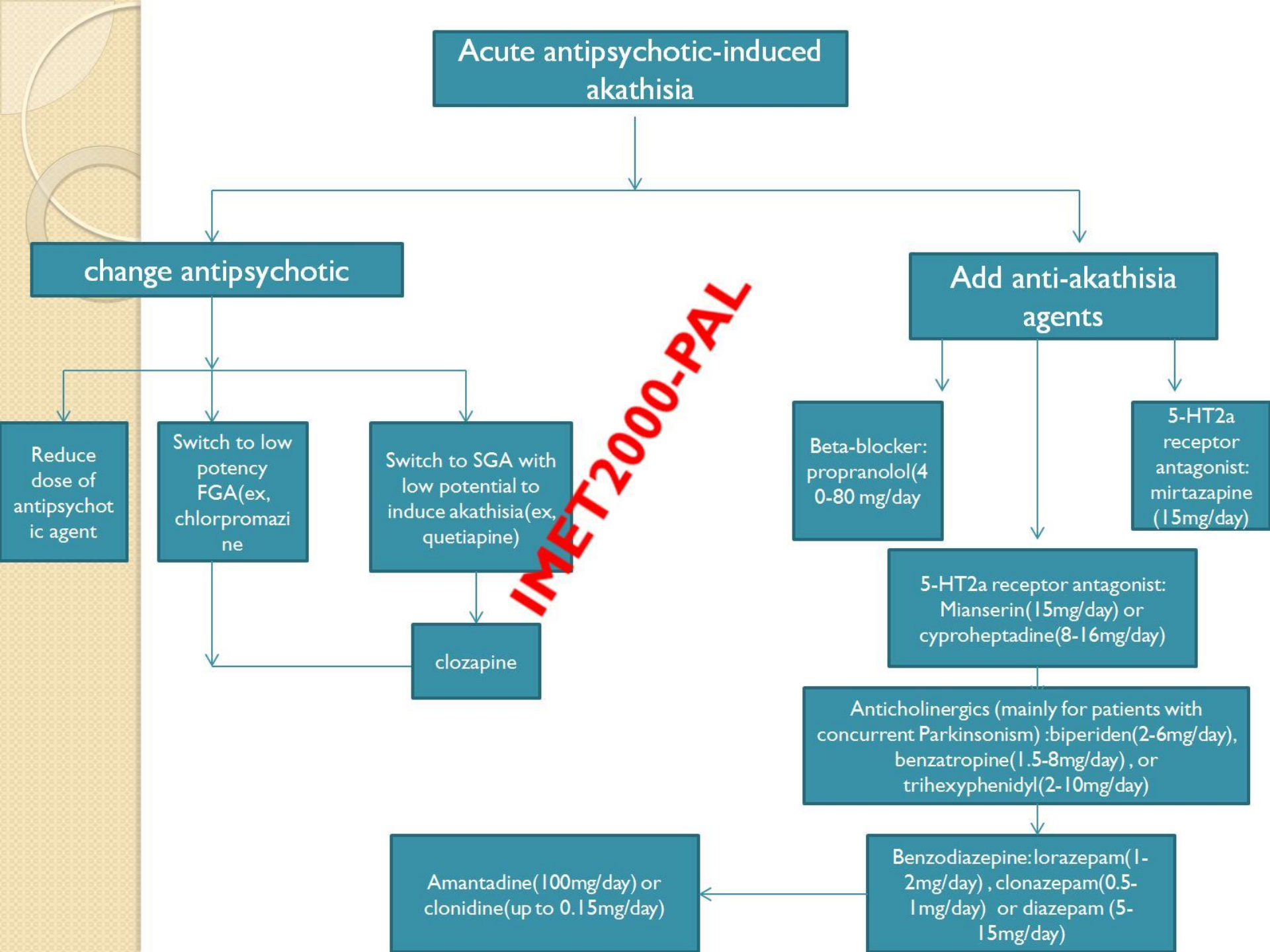
Acute antipsychotic-induced akathisia
change antipsychotic
Add anti-akathisia agents
Reduce dose of antipsychotic agent
Switch to low potency FGA(ex, chlorpromazine
Switch to SGA with low potential to induce akathisia(ex, quetiapine)
clozapine
Beta-blocker: propranolol(40-80 mg/day
5-HT2a receptor antagonist: mirtazapine (15mg/day)
5-HT2a receptor antagonist: Mianserin(15mg/day) or cyproheptadine(8-16mg/day)
Anticholinergics (mainly for patients with concurrent Parkinsonism) :biperiden(2-6mg/day), benzatropine(1.5-8mg/day) , or trihexyphenidyl(2-10mg/day)
Benzodiazepine:lorazepam(1-2mg/day) , clonazepam(0.5-1mg/day) or diazepam (5-15mg/day)
Amantadine(100mg/day) or clonidine(up to 0.15mg/day)
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Why is important?

- Identification of patients treated with SSRI and it's association with **suicidal behavior** highlight it's clinical significant .

- Early detection and rapid amelioration are essential because of risk factor for psychotic exacerbations and non adherence to pharmacotherapy .

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Parkinsonism

- Is **characterized** by symptoms of idiopatic Parkinson which develops insidiously within days or weeks, emerges in 20-40 percent of patients .
- **Cardinal motor symptoms**:

  . Rigidity .

  .Tremor .

  . Bradykinesia (akinesia) , which is unpleasant differential diagnose ,negative symptoms of schizophrenia or depression .

  .Salivation .

  .Gait and balance problem (festinant gait) .
- Rabbit syndrome (perioral tremor) is a form of Parkinson respond well to anticholinergic .

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Treatment

- The first approach is to lower the dose or to change to a lower potency first generation .
- Second , if it doesn't help , an anticholinergic may be added 3-10 days .
- third , if not sufficiently improved symptoms , then a switch to a second generation and antipsychotic .
- It's not good practice to prescribe antiparkinson drug, prophylactic

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Tardive dyskinesia

- Is a polymorphous involuntary movement disorder that usually affects orofaciallingual muscles .
- Onset occurs insidiously over 3 months , affects more than 30 percent of patients and can be irreversible .
- Risk factors include elderly age , female , affective disorder , alcohol , previously brain injury , medical disorder(DM) .
- 5-15% of elderly have spontaneous movements who have never been on antipsychotics .

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Features of Tardive dyskinesia

- Lips , puckering, ponting , smacking .
- Jaw , chewing , biting , side to side movement , jaw opening .
- Tongue , twisting , protrusion .
- Face , grimacing , blinking , frowning .
- Trunk , purposeless , jerky , choreiathetheoid.
- When severe can affect breathing , swallowing , speech .

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Schooler-kane diagnostic criteria for TD

- At least 3 months of cumulative antipsychotic drug exposure.
- Abnormal involuntary movement scale: at least moderate in more than 1 area, or at least mild in more than 2 areas.
- Absence of other casual conditions.
- Probable TD: meets criteria 1 through 3
- Masked TD: meets criteria 1 through 3 but movements suppressed within 2 weeks by antipsychotic drugs
- Transient TD: movements not observed on subsequent examination within 3 months
- Withdrawal TD: movements observed within 2 weeks of antipsychotic drug discontinuation .
- Persistent TD: movements persist for 3 months .

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Features that differentiate

	Tardive dyskinesia (TD)	Drug-induced parkinsonism (DIP)
Onset	late	early
Type of movement	choreoathetoid	Tremor
Amount of movement	increased	decreased
Muscle tone	decreased	increased
Most common site	orofacial	extremities
Response to anticholinergics	Tends to worsen	Tends to improve

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Treatment decisions

- If a patient develops TD , psychiatrist need to make several decision .
- **First** , consider tapering any anticholinergic drugs unless acute EPS are prominent or tardive dystonia are present . 60% of TD cases improve after discontinuing .
- **Second** , decide whether antipsychotic could be safely tapered or discontinued ,if can't be tapered ,decide whether to maintain the present antipsychotic or switch to a more or less potent agent .
- **Finally** , whether a trial of adjunctive antidyskinetic drug is warranted .

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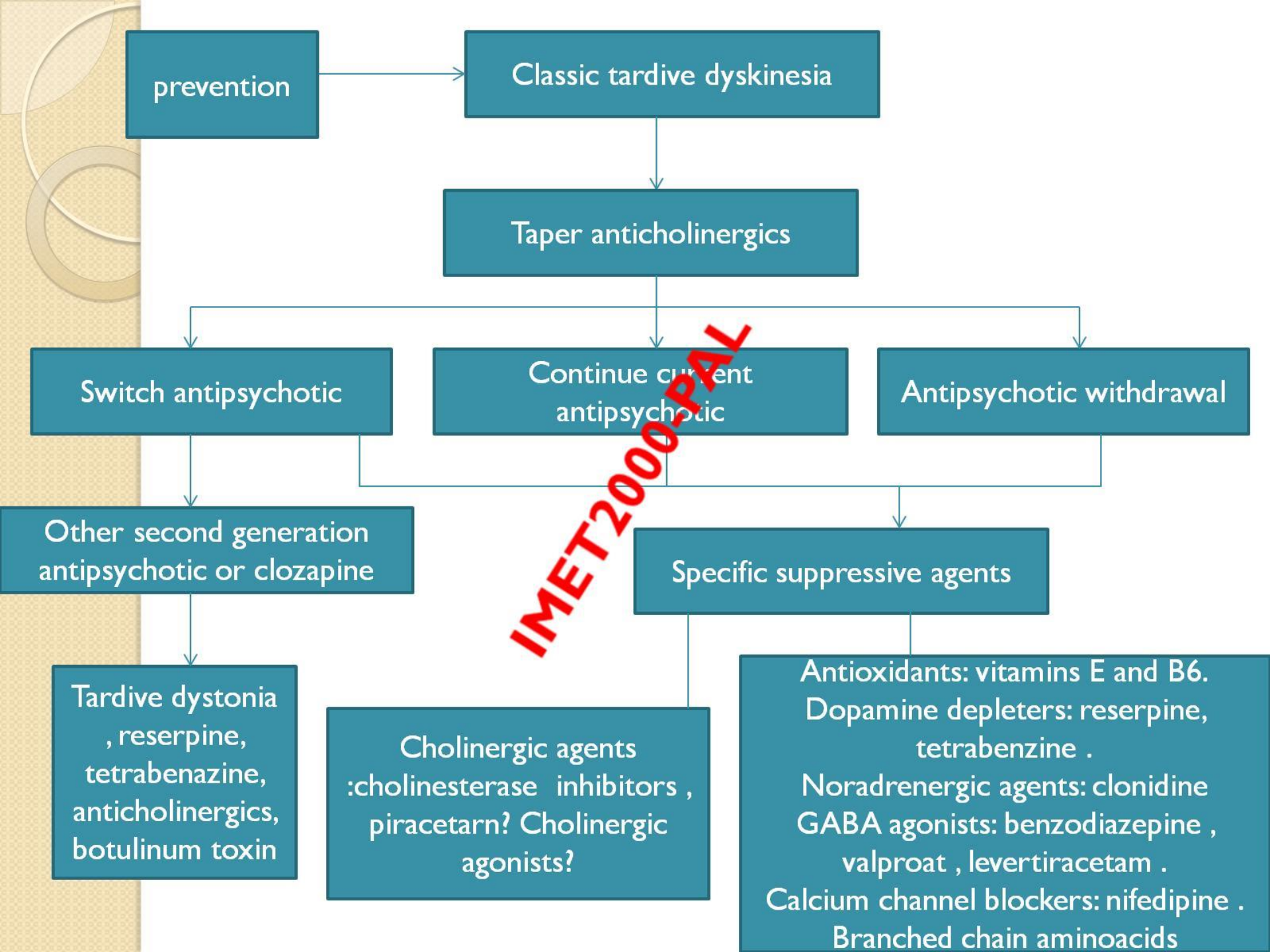

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Management of tardive dyskinesia

- Atypical antipsychotic have radically altered the clinical outlook for patients with TD .
- TD triggered by taking one atypical respond to treatment with another
- Using conventional agents may consider continuing treatment , when patients mental state is satisfactory , TD mild , and no side effects other than TD .
- Complicated TD , clozapine , remains the first line.
- Non antipsychotic agents have come and gone , no one have proven effective (vitamin E, Melatonin , vit.B6, clonidine)
- Non drug treatment (ECT), diet .

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Prevention

- There's no gold standard treatment for TD , it's important to minimize the risk of TD , by taking preventive measures and detecting incipient signs of disorder .
- **Preventive** principles include :

  . Confirming and documenting the indication for antipsychotic .

  . Using conservative maintenance dose and opting for lower potency or newer agents .

  . Informing the patients and carer of risk .

  .Assessing using abnormal involuntary movement scale (AIMS) at least every 3-6 months .

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Tardive dystonia

- Severe variant of Tardive dyskinesia of 4% , which is characterized by sustained spastic contraction of the muscles , begins in most patients in faceornic (80%) .
- The motor presentation are similar to those in acute dystonia and are distinguishable only by duration .
- Oppenheim 1911 introduce the term .
- Burk 1982 coined the term tardive dystonia with classification and criteria .

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Classification

- **Focal dystonia** : only single area of the body is affected :

  . Torticollis

  . Blepharospasm

  . Dysphonia

  . Writer's crump .

  . Orolingual .

- Segmental : . Cranial , axial , brachial , crural.
- Generalized .

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Treatment

- No controlled studies but some patients responds to high dose of trihexphenidyl , dopamine depleting agents (tetrabenazine) large dose of clonazepam , baclofen and deep brain stimulation .
- Botulinum toxin (Botox) can be used in focal dystonia .

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