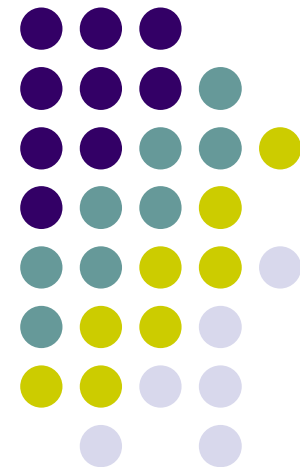


# Diagnosis and treatment of tremors

**XXI WCN    Wien 2013**

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Eduardo Tolosa  
University of Barcelona



# Tremors: phenomenology



- | **Rest**
- | **Action:** postural, kinetic, task specific, isometric

Kinetic tremors can be simple or intentional  
(during target- directed movement)



# Diagnosis of tremors

- | Full clinical history and examination  
(age at onset, mode of onset, site first affected, sequence of spread, etc)
- | Previous and current drug intake
- | Responsiveness of tremor to drugs and alcohol
- | Family history of tremor

# Intestigations



- | Thyroid function
- | Routine hematological, biochemical and toxicological screening
- | Cerebral MR
- | Nerve conduction studies/EMG
- | Genetic studies
- | Dopamine transporter (DAT) SPECT
- | Accelerometry and surface EMG based techniques

# Tremors



## Common tremors

- | Parkinsonian tremors
- | Essential tremor
- | Cerebellar tremor syndromes
- | Drug and toxin induced tremors

## Rare tremors

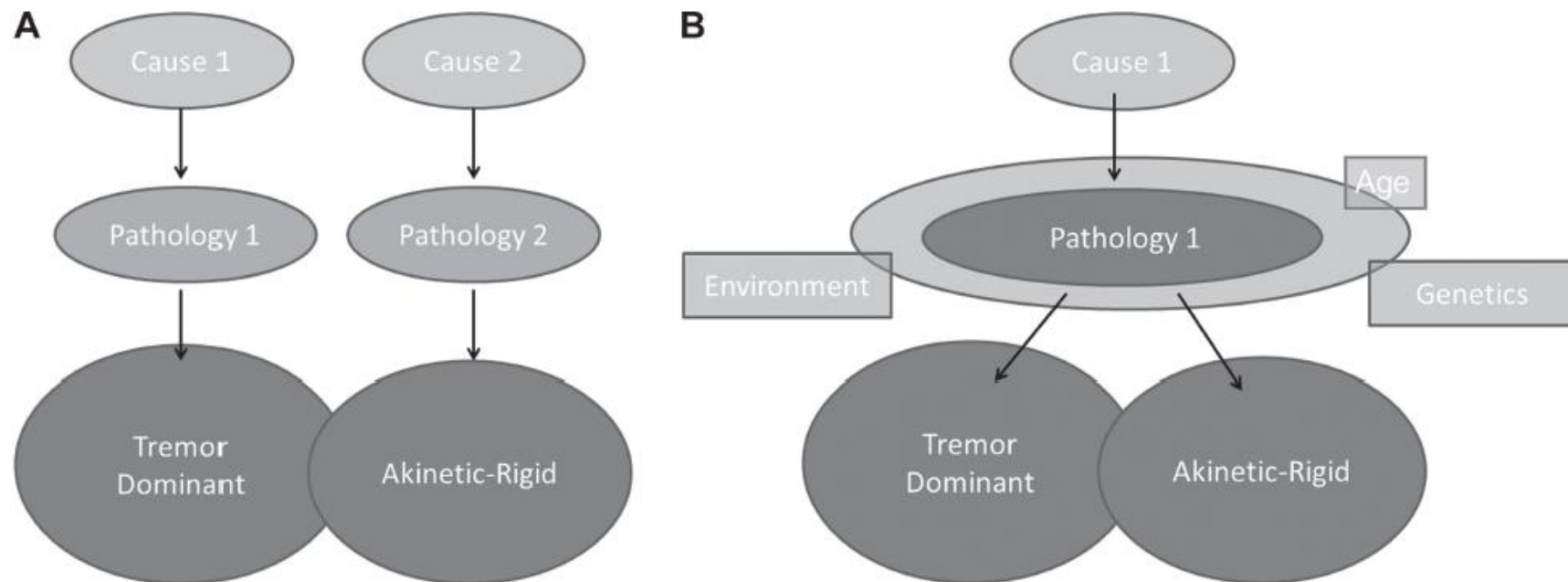
- | Tasks specific
- | Orthostatic tremors
- | Dystonic tremor syndromes
- | Holmes tremors
- | Posttraumatic tremors
- | Neuropathic tremors

# Tremor in Parkinson disease: some facts



- | “pill rolling” rest tremor is characteristic of PD
- | Action tremor is present in many cases
- | Tremor is typically asymmetrical and involves the limbs; less common head or jaw
- | Tremor is the presenting complaint in about 60-70% of cases.
- | Rest tremor may remain the main symptom for years: “tremoric Parkinson disease”

# Parkinson disease subtypes



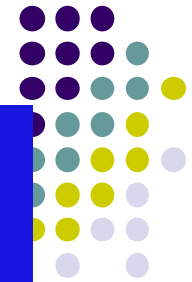
**Figure 1** Possible reasons for distinct subtypes of Parkinson's disease. (A) Subtypes of Parkinson's disease may have separate causes and pathophysiology. (B) Subtypes of Parkinson's disease may share aetiological factors and pathophysiological processes, in which cases patient specific modifying factors (eg, age, environment, genetics) must account for the different manifestations.

# Tremor dominant PD



- | Rest tremor at onset
- | Slow progression
- | Less axial symptoms
- | Less cognitive impairment
- | Respond well to levodopa





**JRG**  
**NHC 663870**  
**8 años evolucion**  
**Datscan alterado bilateral 2010**  
**Exploracion 18/05/2012**

# Neuropathological Findings in Benign Tremulous Parkinsonism

Marianna Selikhova, MD,<sup>1,3</sup> Peter A. Kempster, MD,<sup>1,2,4</sup> Tamas Revesz, MD,<sup>1</sup> Janice L. Holton, PhD,<sup>1,2</sup> and Andrew J. Lees, MD<sup>1,2\*</sup>

**TABLE 5.** Comparison of demographic and pathological data for pathologically proven benign tremulous PD and PD controls

	Benign tremulous PD (n = 15)	PD controls (n = 15)	P
Age at death (y)	83 ± 6.2	82 ± 4.2	NS
Disease duration (y)	24 ± 8.8	22 ± 5.2	NS
Male/female (n)	8/7	10/5	
Mean regional substantia nigra cell loss	2.3 ± 0.4	2.6 ± 0.4	Mann Whitney U: 0.046
Global substantia nigra cell loss	mild = 1; moderate = 9; severe = 5	mild = 0; moderate = 2; severe = 13	χ <sup>2</sup> : 0.003 <sup>a</sup>
Lewy body type	brainstem = 3; limbic = 7; neocortical = 5	brainstem = 0; limbic = 7; neocortical = 8	NS
Braak PD stage	5.7 ± 0.5	5.9 ± 0.4	NS
Braak and Braak neurofibrillary stage	1.7 ± 1.2	1.5 ± 0.6	NS
Amyloid-β grade, diffuse deposits	0.8 ± 0.8	1.5 ± 1.2	NS
Amyloid-β grade, mature deposits	0.6 ± 0.8	0.9 ± 1.0	NS
Cerebral amyloid angiopathy grade	0.3 ± 0.6	0.7 ± 1.1	NS
Cerebrovascular disease grade	0.7 ± 0.5	0.7 ± 0.7	NS

Mean statistics shown with standard deviations. Pathological stages, grades, and typing as defined in Pathological Methods.

<sup>a</sup>Mild or moderate compared with severe cell loss.

PD, Parkinson's disease; NS, not significant.



**Dear DR.**

At present I am not on any medication. I have been diagnosed with PD for 13 months now. My main symptom, although I have others, is shaking of the right hand and now also of the right leg (less than in hand).

My doctor has suggested starting me on Requip because of my age (50).

**What medication, in your opinion, is the best medication for tremors?**

Thank you, Marie

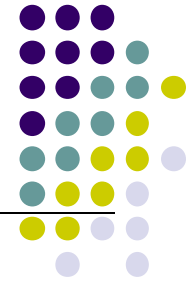
**answer**

**no medication hones in like a guided missile on a single symptom**

given your age the choice of Requip or Mirapex is a good starting point

# DBS and Parkinson tremor

---



- | STN-DBS lessens tremor severity about 80% ( vs 50% akinesia)
- | The effect on tremor is immediate. In some cases there is a gradual build-up of effect over time.
- | The effect on tremor may go beyond the effect of levodopa
- | STN/GPi rather than Vim are the preferred targets for Parkinsonian tremor because they also ameliorate akinesia and rigidity
- | Side effects acceptable but potentially serious



# **BILATERAL SUBTHALAMIC STIMULATION**



Unilateral leg tremor at onset is common in parkin and LRRK2-PD (24% vs 3% in iPD)

# Classical essential tremor



- | A monosymptomatic, predominant action tremor (postural and kinetic) which is usually slowly progressive over years.
- | Frequently familial
- | Mean age at onset 35-45 years with almost complete penetrance at the age of 65 years
- | 50 -90 % improve with the ingestion of alcohol

# Secondary criteria



- | Long duration (> 3 years)
- | Positive family history
- | Beneficial response to ethanol





# Essential tremor

- | The hallmark feature of ET is a kinetic tremor (i.e., tremor that occurs during voluntary movement) of the arms
- | ET traditionally regarded as a benign, mono-symptomatic condition

# Essential tremor



- | all the patients are disabled to some extent
- | most are socially handicapped
- | Up to 25% of the patients seeking medical attention must change jobs or to retire from work .

# Classical ET topography



- | hand tremor in 94%, head tremor in 33%, voice tremor in 16%, jaw tremor in 8%, facial tremor in 3%, leg tremor in 12% and tremor of the trunk in 3% of the patients

(Elbe et al Neurology 2000)

- | tremor may occur in isolation in the head, chin and voice.
- | intention tremor occurs frequently
- | rarely even resting tremors do occur







# Red flags



- | Onset after age 65
- | Unilateral tremor, symptomatic tremor in the trunk or lower limbs, rest tremor
- | Relative or absolute position or task specificity
- | Sudden or rapid onset
- | Current drug treatment that might cause or exacerbate tremor
- | Isolated head tremor with abnormal posture (head tilt or turning)

# Essential tremor: additional motor and non motor symptoms



- | Disturbances in tandem walking
- | Hearing deficits
- | Cognitive deficits
- | Anxiety and depression



# Evidence for a pancerebellar dysfunction in ET

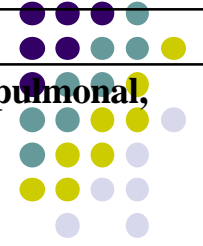


- | Intention tremor (a sign of impaired cerebello-thalamic function)
- | Hand and arm dysmetria (neo-cerebellum)
- | Gait and stance abnormalities (spino-cerebellum)
- | impairment of ocular smooth pursuit initiation and abnormal suppression of the vestibulo-ocular reflex (vestibulo-cerebellum)

# Etiology of essential tremor



- | Cerebellar neurodegenerative process?
- | Disturbance of cerebellar function secondary to longstanding abnormal neuronal oscillation?
- | Young versus old onset ET ?
- | Many cases Mendelian autosomic dominant; several candidate disease loci but no specific genes identified

	drug	dosage	remarks	
1 <sup>st</sup> choice	Propranolol	(30-320 mg, 3 doses) (standard or long-acting)	Contraindications: cardiac, pulmonary, diabetes etc. Hand and head tremor	
1 <sup>st</sup> choice	Primidone	(62,5 –500 mg, single dose in the evening)	Hand and head tremor Preferentially for patients with age > 60 years	
1 <sup>st</sup> choice	Combination: Propranolol/ Primidone	maximum dosage for each.	Try always before using 2 <sup>nd</sup> and 3 <sup>rd</sup> choice drugs	
2 <sup>nd</sup> choice	Gabapentine	1800 – 2400 mg daily	Conflicting results of three db-studies: one without, two with benefit!	
2 <sup>nd</sup> choice	Topiramate	< 400 mg	So far small db-study only	
2 <sup>nd</sup> choice	Clonazepam	0.75 – 6 mg	For predominant kinetic tremor	
3 <sup>rd</sup> choice	Botulinumtoxin		Db-study with a significant result, but weakness as a significant side effect	
3 <sup>rd</sup> choice	Clozapine	Test:: 12,5 mg, 30-50 mg daily	Less well documented effect than for Parkinson's disease. Often ineffective	
Last choice	surgery		Vim or caudal zona incerta stimulation or thalamotomy	

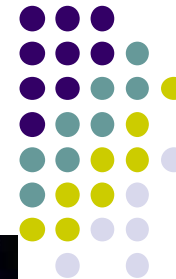


## Deep Brain Stimulation and Tremor

Kelly E. Lyons and Rajesh Pahwa

*Parkinson's Disease and Movement Disorder Center, Department of Neurology, University of Kansas Medical Center,  
Kansas City, Kansas 66160*

**Summary:** Deep brain stimulation (DBS) has been used to treat various tremor disorders for several decades. Medication-resistant, disabling essential tremor (ET) is the most common tremor disorder treated with DBS. The treatment has been consistently reported to result in significant benefit in upper extremity, as well as head and voice tremor, all of which were improved more dramatically with bilateral procedures. These benefits have been demonstrated to be sustained for up to 7 years. DBS has also been shown to be beneficial for the tremor



10 ANYS ABANS



# Essential tremor variants

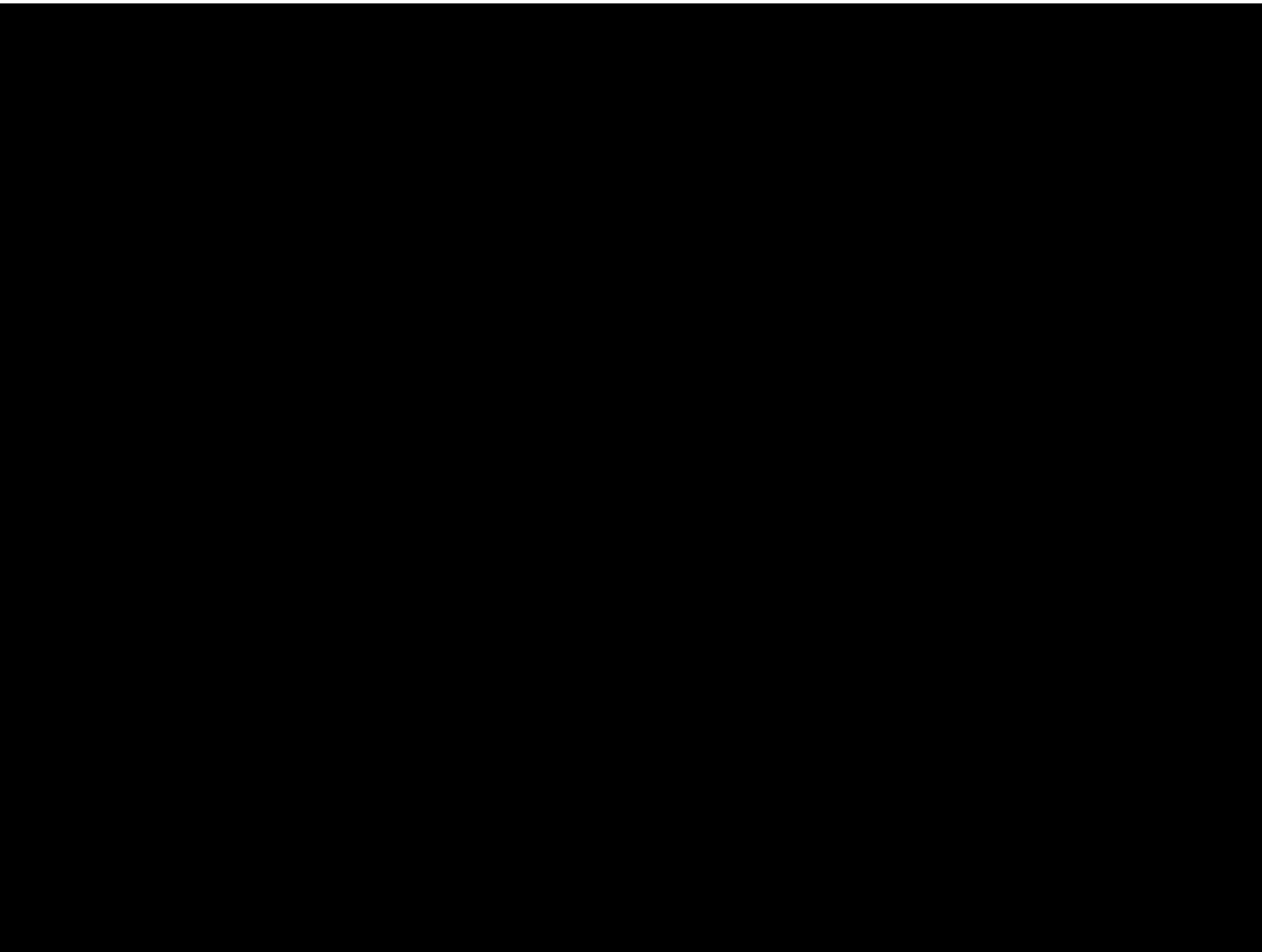


- | task/position specific tremors (e.g. primary writing tremor)
- | Isolated voice tremor
- | Isolated chin tremor
- | Primary orthostatic tremor

# Task or position specific tremors



- | Tremor may occur only during the performance of specific tasks (task-induced tremor) or postures (positionally sensitive tremor).
- | The most common example is **primary writing tremor**
- | Similar task-specific tremors can affect other fine tasks, for example playing a musical instrument.
- | Other skilled movements (eating, handling delicate objects etc.) remain mostly unaffected







A.G.C

NHC: 77980

Unidad de Trastornos del Movimiento

Hospital Clinico de Barcelona

19-Febrero-2008

# Task or position specific tremors



- | Focal forms of essential tremor?
- | Focal dystonias?
- | Specific overuse syndromes?
- | Treatment is difficult. Propranolol, primidone, anticholinergics and local injections of botulinum-toxin have been proposed.
- | Thalamic DBS?

# Primary orthostatic tremor



- | Middle aged individual of either sex
- | Tremor of the legs and trunk on standing
- | Starts shortly (secs to minutes) after standing
- | Complains of unsteadiness, leg shakes on standing; occ. cramps, falls. Worse with fatigue and stress
- | Relieved by walking, sitting, lying or leaning against support
- | Tremor may not be visible on naked eye but is felt by the examiners hand as a ripple
- | Family history of essential tremor may be present

# Primary orthostatic tremor

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- | Wide spectrum of frequencies: 13 to 18 Hz
- | Highly synchronized discharges in corresponding leg (and arm) muscles
- | Tremor frequency can change when changing activity
- | **TREATMENT:** + responses to clonazepam, gabapentin, phenobarbital or primidone

# ORTHOSTATIC TREMORS



## **PRIMARY ORTHOSTATIC TREMORS**

## **SECONDARY (or symptomatic) ORTHOSTATIC TREMORS**

**essential tremor**

**Parkinson's disease**

**Hyperthyroidism**

## **OTHER INVOLUNTARY MOVEMENTS OCCURING WHEN STANDING**

**clonus**

**cerebellar ataxia**

**myoclonus**

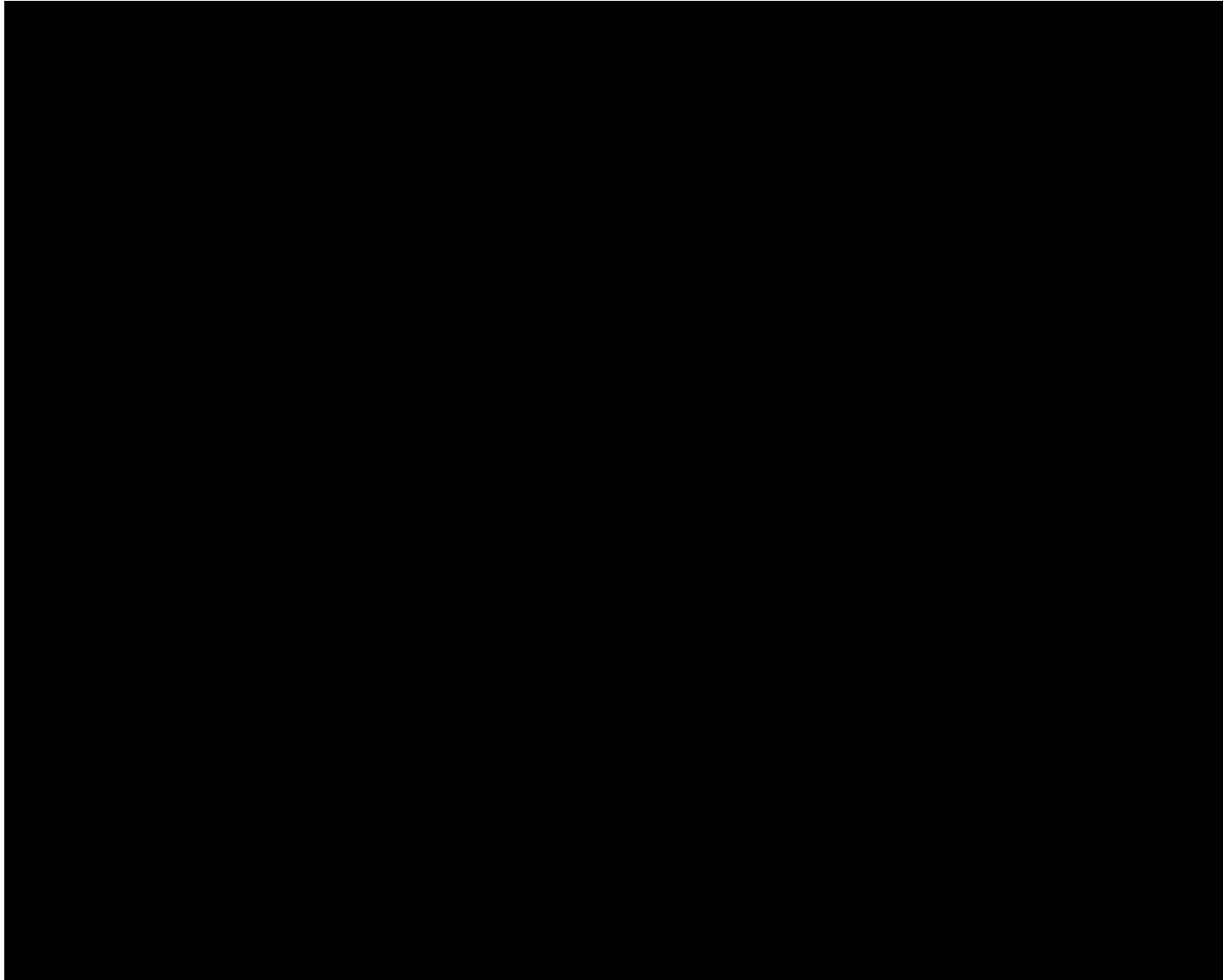
**akathisia**

# Tremors and dystonia



- | **Dystonic tremor** is defined as a postural/kinetic tremor usually occurring in an extremity or body part which is affected by dystonia.
- | Usually these are focal tremors with irregular amplitudes and variable frequencies (mostly below 7 Hz).
- | **Tremor associated with dystonia** occurs when tremor occurs in a body part that is not affected by dystonia but dystonia is present elsewhere.
- | It is clinically indistinguishable from enhanced physiological or essential tremor

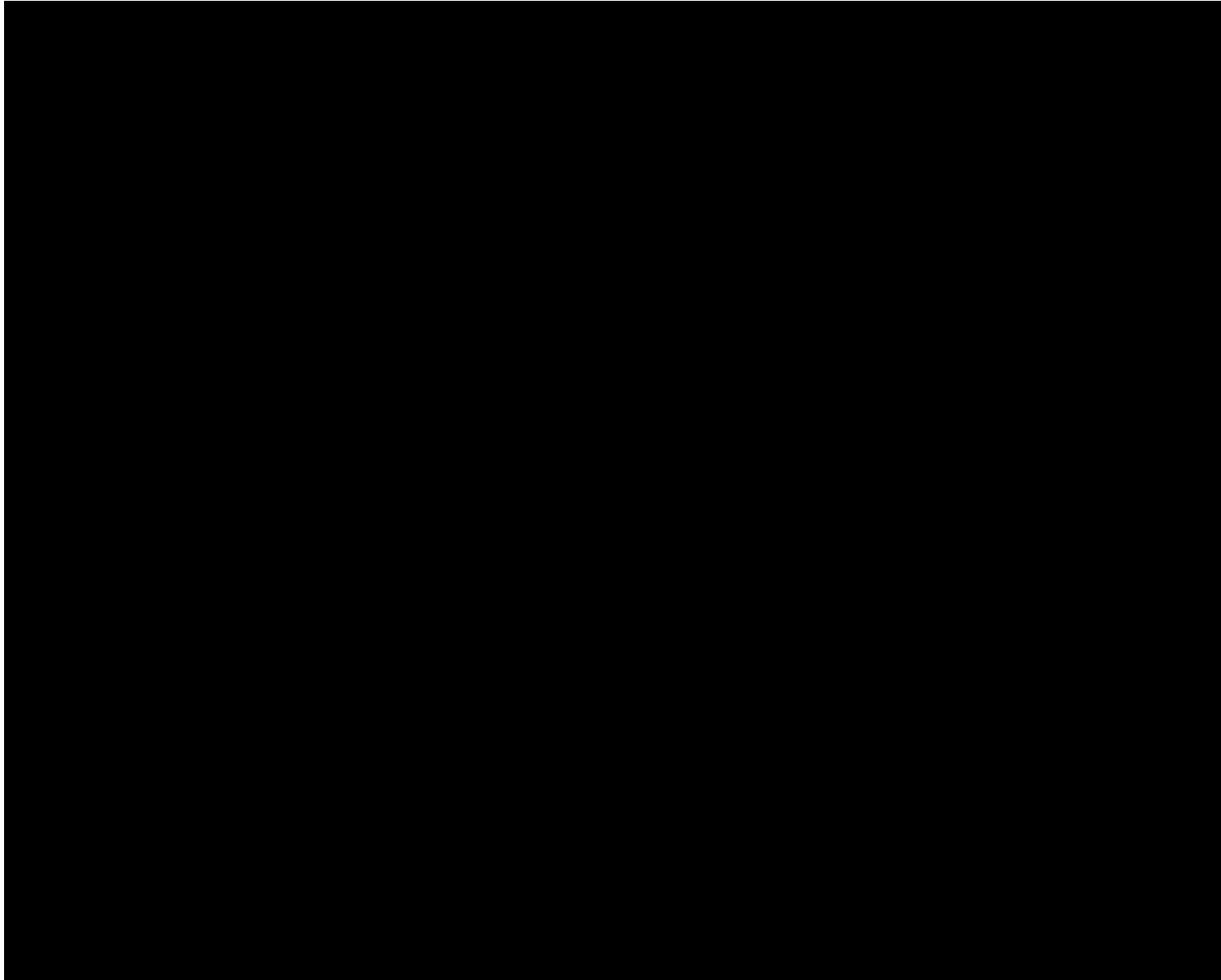
# Adult onset cervical dystonia



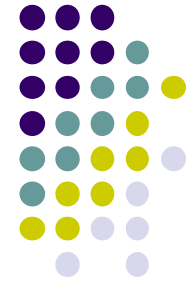
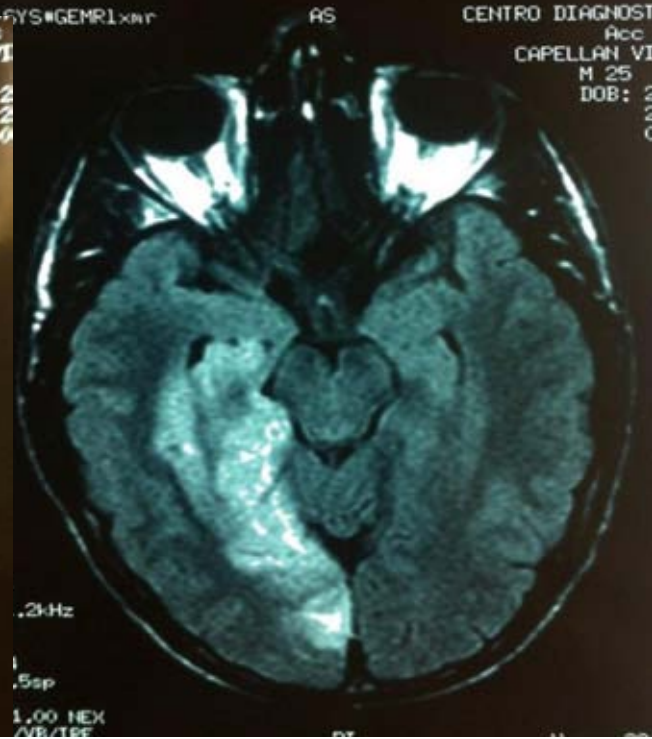
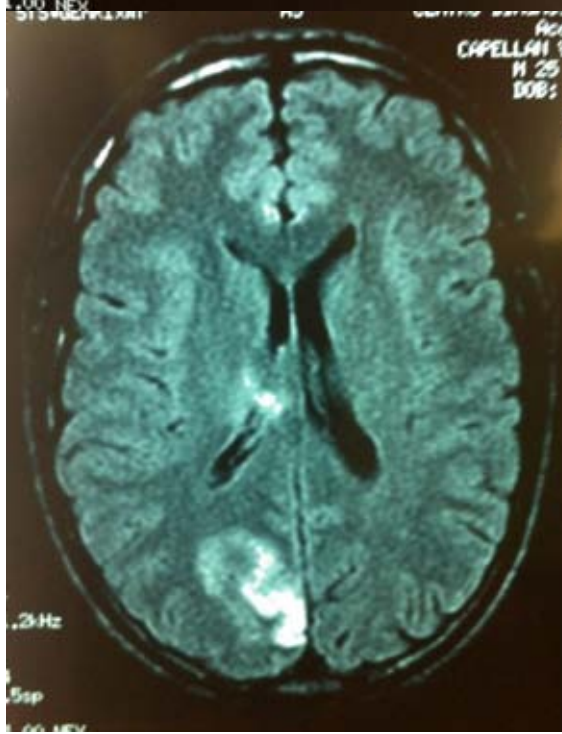
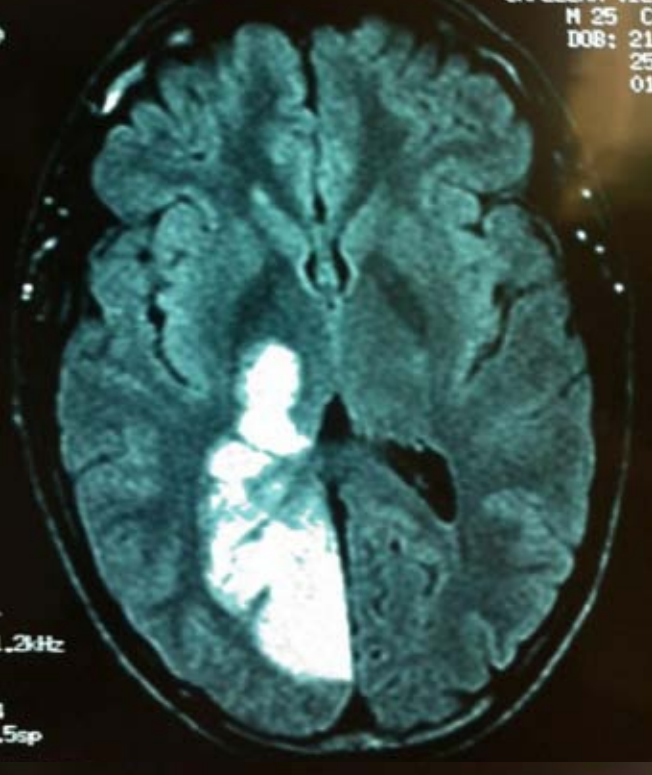
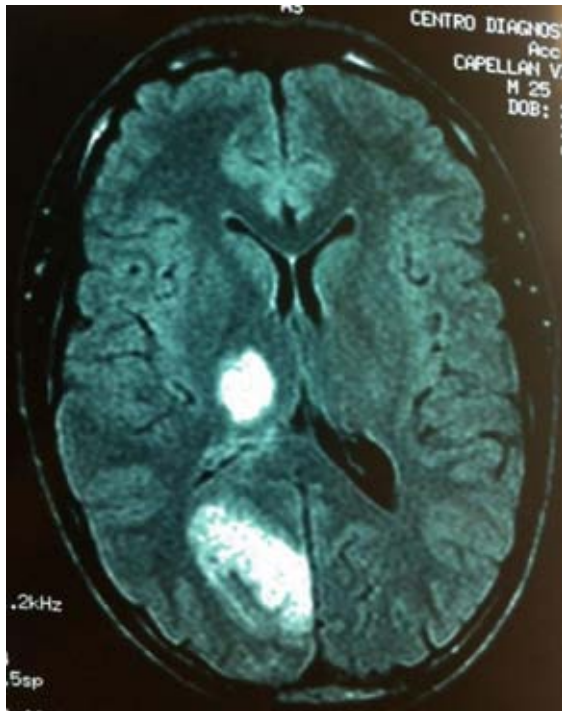


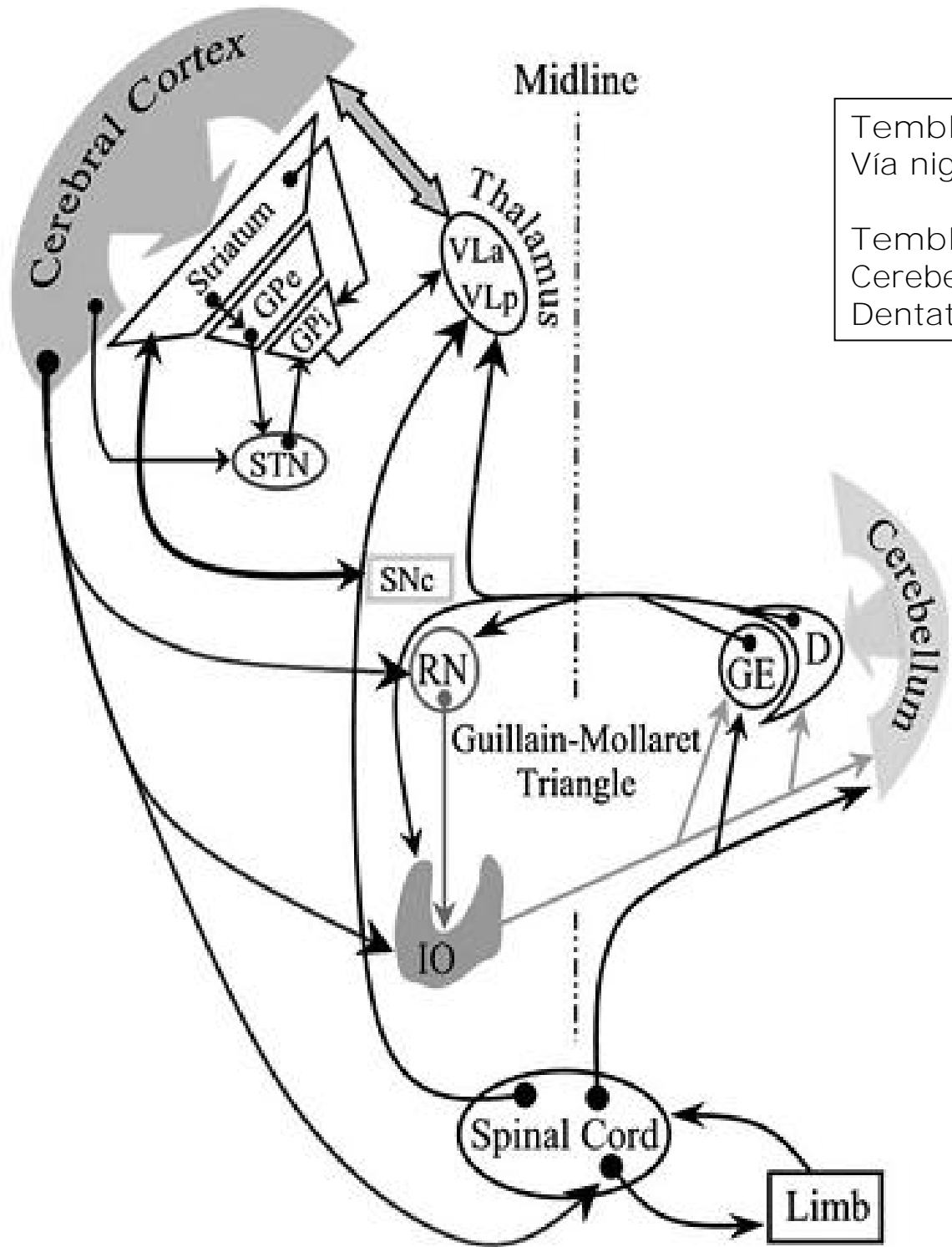


# Isolated tongue tremor









Temblor reposo:  
 Vía nigroestriatal

Temblor de acción:  
 Cerebelo-tálamo-cortical  
 Dentato-rubro-olivar

# Isolated head tremor





THANK YOU FOR YOUR INTEREST !!



# Holmes tremor (midbrain tremor; rubral tremor)



- | Combination of rest (4.5 Hz) and action tremor
- | Lesions in the vicinity of the red nucleus, which may disrupt the nigrostriatal pathway, (rest tremor), and cerebellothalamic fibres, (action tremor)
- | Stroke, vascular malformations, trauma or tumors
- | Levetiracetam and contralateral thalamic (Vim) stimulation reported useful in some cases





**Table 1. Medication induced tremor**

Group	Medication	Tremor character
Antiarrhythmic	Amiodarone	Clinically similar to essential tremor, 6–10 Hz action tremor
Antidepressant	Tricyclic, serotonin re-uptake inhibitor, monoamineoxidase inhibitor	Generalized action tremor, 6–11 Hz
Beta adrenergic agents	Terbutaline, metaproterenol, isoetharine, epinephrine, adrenaline	Rest and action tremor, low amplitude and high frequency
H2 antagonist	Cimetidine	Action tremor 8–12 Hz
Calcineurine inhibitor	Ciclosporine A	Generalized action tremor, rarely cerebellar tremor; treatment with propranolol
Anticonvulsant	Lamotrigine	Postural and action tremor
	Valproate sodium	Rest and postural tremor
Neuroleptics	Lithium	Irregular, not rhythmic tremor in arms/legs; treatment with primidone/ $\beta$ -blocker
Antipsychotics	Low- and high potent (i.e. Haloperidol, Clozapine)	Rest and postural tremor 4–7 Hz; tardive tremor as postural tremor 3–5 Hz; asterixes
$\beta$ adrenergic Inhibitors	Pindolol	Low amplitude, high frequency tremor
Antiobstructive agent	Theophylline	High frequency, low amplitude postural tremor
Triazole antifungal agent	Itraconazole	Heterogeneous, from 4–6 Hz to 12–15 rest tremor

# Other tremors



- | Drug and toxin induced tremors
- | Holmes tremor (midbrain tremor)
- | Psychogenic tremors
- | Posttraumatic tremors
- | Neuropathic tremors
- | Tremors in systemic disorders









R.B. NHC: 4287601  
Unidad de Trastornos del Movimiento  
Hospital Clinico de Barcelona  
15-Julio-2008



# Common tremors

- | Parkinson tremors
- | Enhanced physiological tremors
- | Essential tremor
- | Cerebellar tremor syndromes
- | Drug and toxin induced tremors

# Rare tremors

- | Tasks specific
- | Orthostatic tremors
- | Dystonic tremor syndromes
- | Holmes tremor (midbrain tremor)
- | Stroke related tremors
- | Posttraumatic tremors
- | Neuropathic tremors
- | Tremors in systemic disorders







University of Pennsylvania | Perelman School of Medicine | HCP

Name: LEWIS      Room: 1521 OS

IPIC:

Diagnosis: PARVAIRN DISEASE

TREATMENT: PARLOVELS 1-1-2  
PLURINENS 1-1-0

