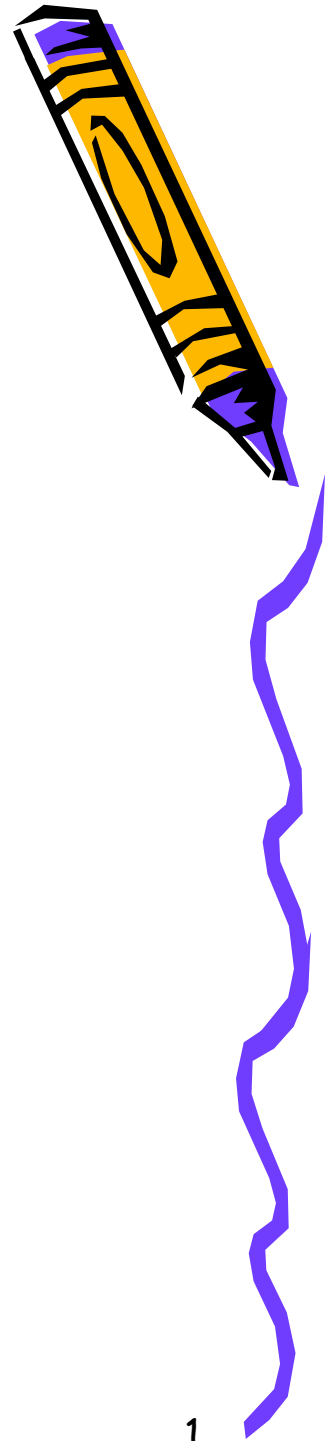


# Tourette's Disorder

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# Question 1

A 12 year old boy has phonic tics for 8 months and no motor tics. What is the appropriate diagnosis?

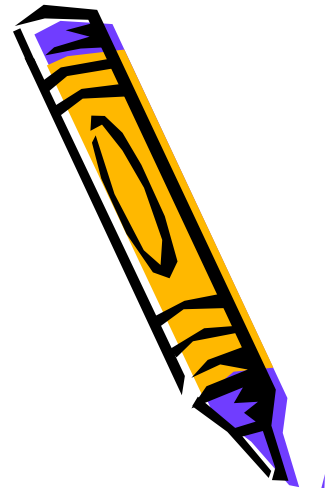
- A) Chronic phonic tic disorder
- B) Transient phonic tic disorder
- C) Tourette's Syndrome
- D) Syndenham Chorea



# Question 2

A 10 year old boy meets diagnostic criteria for Tourette's Disorder. He also has co-morbid ADHD. What is the initial drug of choice to treat the latter symptoms?

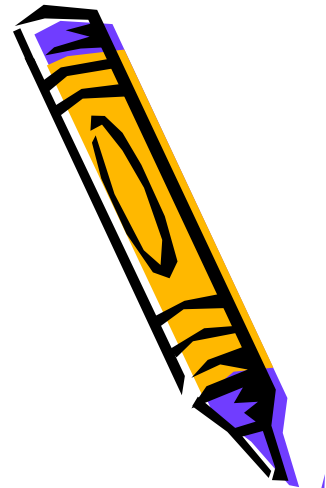
- A) Risperidone
- B) Guanfacine
- C) Atomoxetine
- D) Psychostimulants



# Question 3

The behavioral intervention that may have promising results for treating Tourette's Disorder is:

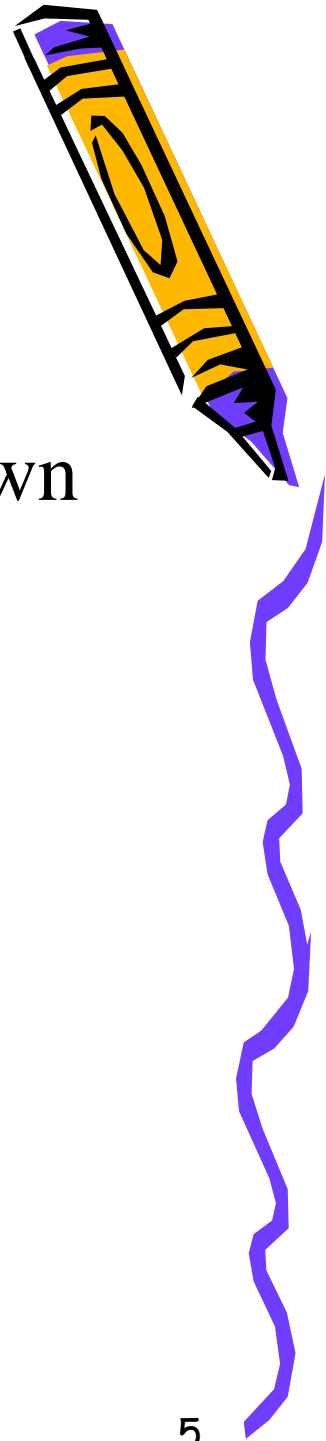
- A) Token Economy
- B) Habit Reversal Training
- C) Systemic Desensitization
- D) Flooding



# Question 4

All of the following medications have been shown to be effective in reducing tics EXCEPT:

- A) Haloperidol
- B) Clozapine
- C) Clonidine
- D) Risperidone



# Question 5

Which of the following statements are true of TD?

- A) Coprolalia must be present to make a diagnosis
- B) Tics generally improve during adolescence
- C) Motor tics generally appear later than vocal tics
- D) A diagnosis of TD requires a symptom duration of 2 weeks



# Teaching Points

- Childhood onset neuropsychiatric disorder with chronic motor and vocal tics
- Common comorbid disorders include ADHD, OCD, anxiety disorders and mood disorders
- Mild to moderate tics improve with behavioral management; medications only for persistent, painful or impairing tics



# Tourette's Disorder (TD)

- Developmental neuropsychiatric disorder with childhood onset.
- Chronic motor and vocal tics
- Brief, stereotypical, nonrhythmic movements and vocalizations
- Usually begins with motor tics between age 3-8 years





# Epidemiology

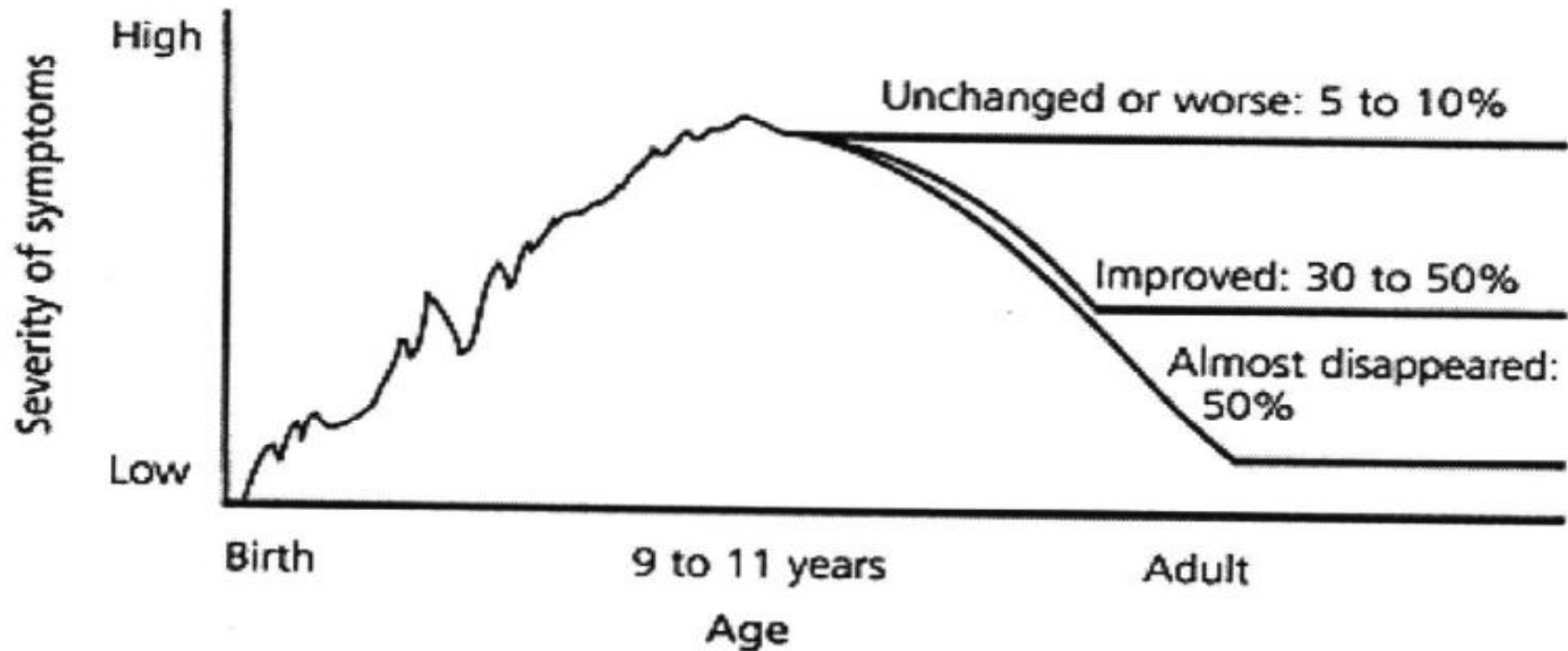
(Robertson 2003)

- TD prevalence (DSM-IV) = 4-5/10,000
- Motor tics begin between the ages 3-8 years
- Four times more common in males vs. females
- Tic severity greater bet'n age 7-12 years; wanes by age 20
- 20% children with TS continue to experience a moderate level of impairment of global functioning by the age of 20 years
- Waxing & waning pattern of severity, intensity & frequency



# Leckman 1998

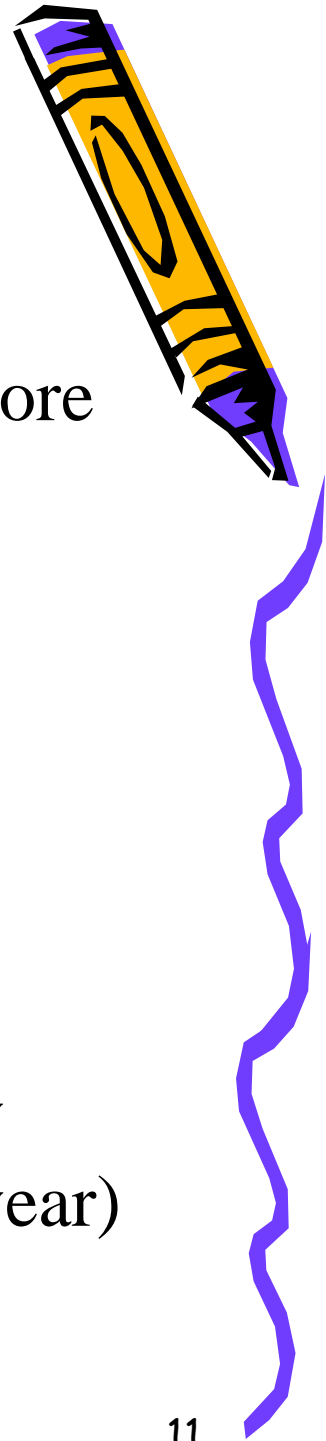
## Clinical Course of Tourette's Syndrome



**FIGURE 1.** The clinical course of Tourette's syndrome. Onset typically occurs before seven years of age and the disorder is usually recognized two to three years after onset. In most children, the severity peaks at nine to 11 years of age. About 5 to 10 percent of patients have an intensifying course with little or no improvement. In about 85 percent of patients, symptoms diminish during and after adolescence.

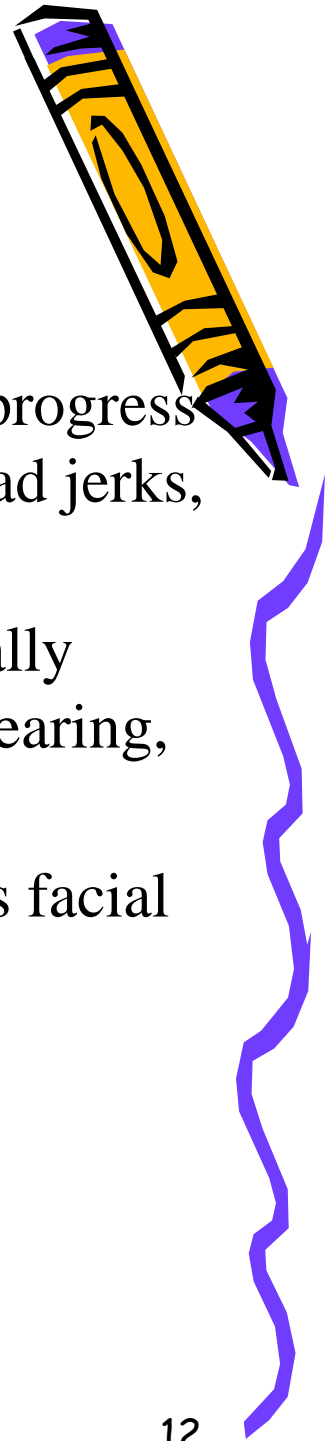
# DSM-IV-TR Criteria for TD

- Fluctuating course of multiple motor and one or more vocal tics
- Tics many times a day for >1 year
- Variable locations & frequency of tics over time
- Onset before 18 years (typical range 2- 15 years)
- Exclude substance abuse and CNS diseases like Huntington Chorea, postviral encephalitis
- Exclude common transient motor or phonic tics by duration (Tics for at least 4 weeks but less than a year)



# Common variants

- Simple motor tics: Usually involve eyes, face, or head; may progress to shoulders, trunk, and extremities. Include eye blinking, head jerks, or shoulder shrugs
- Simple phonic/vocal tics: Sounds, noises, or utterances. Usually begin years after onset of motor tics. Include simple throat clearing, grunting, and squeaking
- Complex motor tics: Purposeful-appearing behaviors, such as facial expressions or gestures, possibly dystonic movements
- Complex vocal tics: Echolalia, Palilalia, Coprolalia



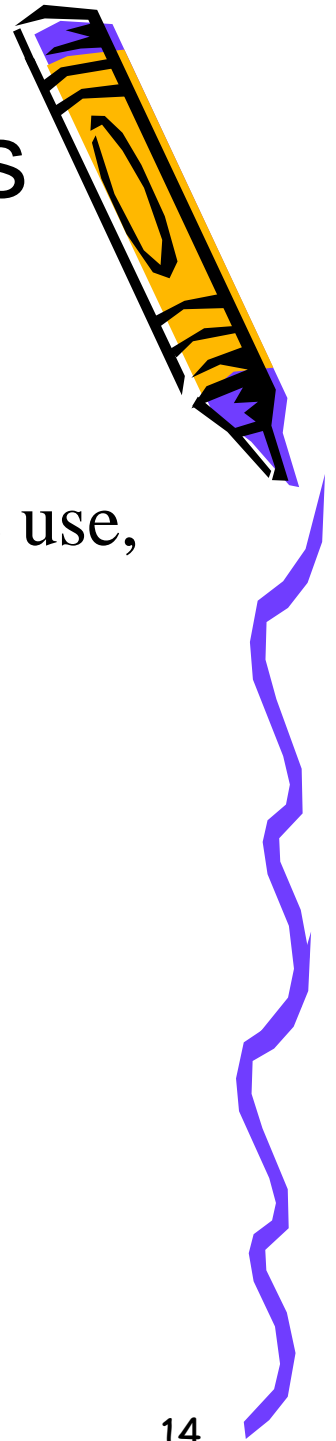
# Clinical Features

- Partial voluntary control
- Antecedent sensory phenomena, general sense of inner tension or focal “premonitory urges.”
- Bouts are 0.5-1.0 sec, brief periods of stable inter-tic intervals
- Sensitive to psychosocial stress, anxiety, emotional excitement & fatigue
- Activities needing focused attention and fine motor control may transiently decrease tics; diminished during sleep



# Secondary Causes of Tic Disorders

- Metabolic – Wilson’s disease, Hyperthyroidism
- Trauma - Head trauma
- Toxic – Amphetamine abuse, Cocaine abuse, Neuroleptic use, L-Dopa (phonic), CO, Manganese
- Infectious - Viral encephalitis, Sydenham’s chorea, Post streptococcal infections
- Neoplasm - Basal ganglia tumors
- Neurological - Mitochondrial encephalomyopathy, Parkinsonism, Huntington’s chorea, Neuroanthocytosis, Meige’s syndrome



# Comorbidity with TD

(Swain 2007)

- ADHD 60-70%; can be associated with disruptive behaviors: comorbid ADHD → academic difficulties, peer rejection & family conflict
- OCD: 50% of patients with TD may have obsessive-compulsive features.
- Anxiety disorders 20-30%
- Mood Disorder 20-30%
- Learning disorders 20-30%
- Fourfold increase in migraines



# Etiology

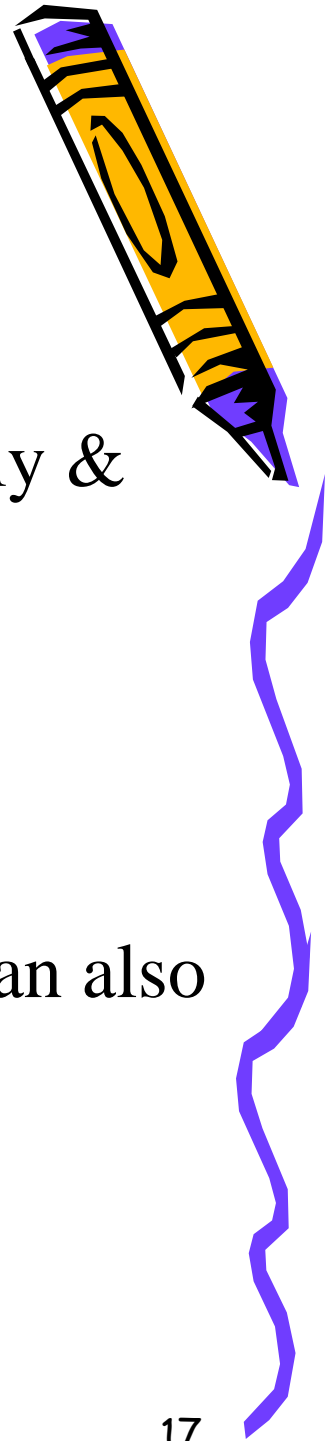
- Stress Diathesis model: Genetic-environmental interaction
- Heightened reactivity of HPA axis & sympathetic systems
- Genetic: Monozygotic twins > Dizygotic twins; association with 11q23, 4q, 8p regions; disruption of contactin associated protein 2 gene; Gene SLITRK1 possible candidate gene, genes for DA, NA, 5-HT receptors
- Environmental factors: Perinatal hypoxia, Exposure to androgens, heat & fatigue, Post-infectious autoimmune (Gp-A  $\beta$ -hemolytic Streptococci)
- Patients with TS more likely had streptococcal infection in 3 months before onset date; risk more with multiple strep. infections in past 12 months





# Assessment

- Assess degree to which tics interfere with child's emotional, social, family & school experiences
- Thorough perinatal, medical, developmental, family & psychosocial history
- Look for comorbidities: ADHD, OCD, Learning disability
- Quantification of tic severity with Yale Global Tic Severity Scale; TS Diagnostic Confidence Index can also be used
- Exploration of child's strengths and qualities



# General Principles for Medication use for tics

- Start with low doses and go slow
- TD has variable tic frequency over time; may be difficult to assess efficacy against fluctuating symptoms
- Use a pre-treatment scale to assess comorbidity & severity eg: CYBOCS, ADHD scales, Yale Global Tic Severity Scale
- Use videotaping of tics- Rush Video Rating Scale
- Be patient, do a thorough treatment trial
- May need to use medication to treat tics during pre-teen years

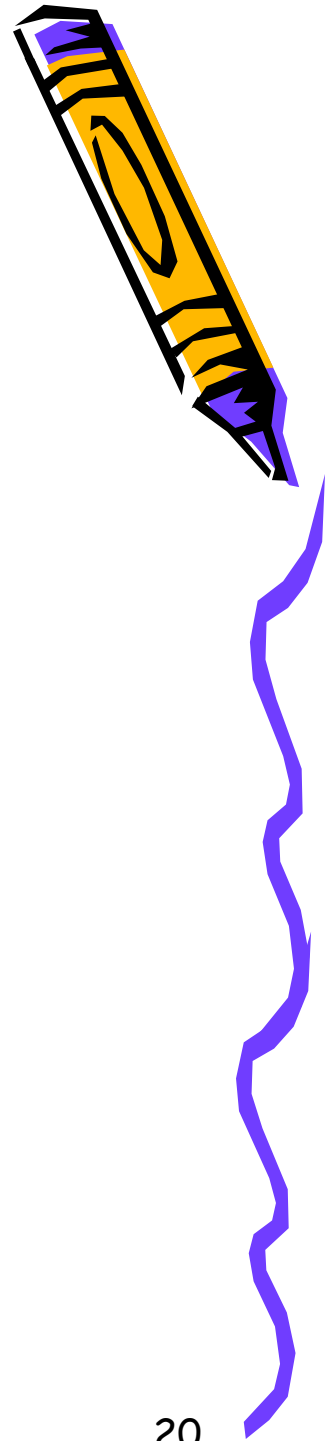


# Treatment

- Treat at least moderate to severe tics with evidence of impairment in interpersonal spheres/self esteem
- Treat comorbidity first: may ↓ tic severity
- May be best initiated with educational and lifestyle measures before medication use
- Educational interventions: Enhanced awareness for patient, family & peers; advocacy groups: Tourette Syndrome Association, collaboration with schools.
- Lifestyle changes aimed at reducing stress; Stress management
- Behavioral management: Habit-reversal training is promising; CBT for OCD



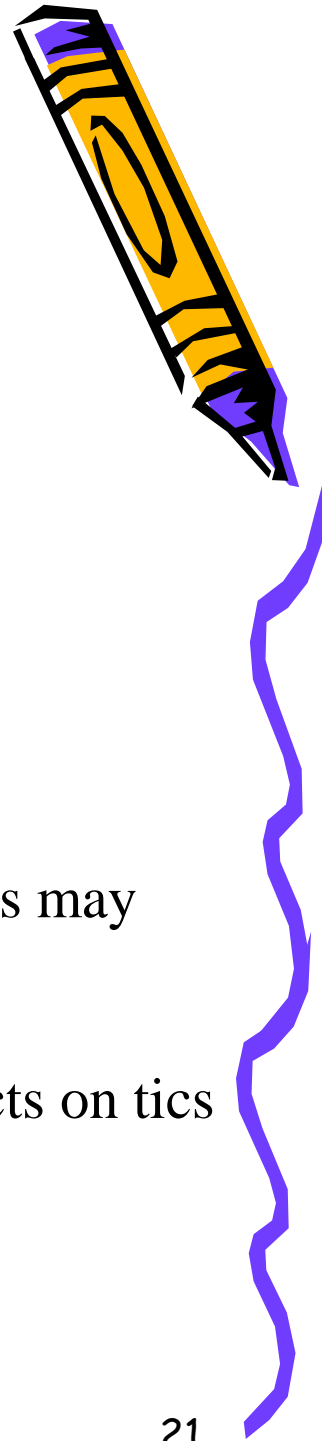
# Indications for medication use for tic disorders:



- Persistent tics
- Functional impairment
- Social impairment (of the child, not the parents)
- Classroom disruption
- Pain



# Psychopharmacology for TD



Tics  
Clonidine/Guanfacine  
Risperidone &  
other atypicals  
Haloperidol  
TCAs  
Pimozide  
Clonazepam  
Pergolide

ADHD/Impulsivity  
Psychostimulants  
Atomoxetine

Clonidine/Guanfacine

OCD and Anxiety  
SSRIs  
Clomipramine  
Clonazepam

- Bupropion, Imipramine, Chlorpromazine, Thioridazine, Antihistamines may worsen tics
- Clozapine was found to be ineffective in TD
- SSRIs may have indirect effect by reducing inner tensions but no effects on tics directly



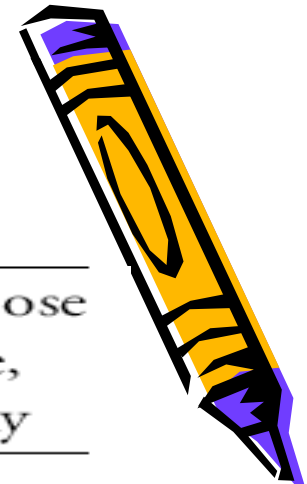
# Combined Data for improvement in tics (YGTSS) in children with TD from DBPC studies (\*active drug-placebo)

- Metoclopramide 26% (Nicolson et al 2005)\*
- Desipramine 30% (Spencer 2002)\*
- Guanfacine 31% (Scahill 2001)\*
- Risperidone 25% (Scahill 2003)\*
- Levetiracetam No difference (Smith-Hicks 2007)
- Ondansetron No difference (Toren 2005)
- Mecamylamine No difference (Silver 2001)
- Baclofen No difference (Singer 2001)
- Fluoxetine No difference (Scahill 1997)



# Psychopharmacology for TD

(Swain 2007)



Medication	Empiric Support	Starting Dose, mg	Usual Dose Range, mg/day
<b>Nonantipsychotics</b>			
Clonidine	B	0.025–0.05	0.2–0.4
Guanfacine	B	0.5–1	2–4
Pergolide	B	0.025 every 2 days	0.15–0.45
Botulinum toxin A	B	Motor tics: 50–75 U Vocal tics: 1–2.5 U	75–250 1–2.5
<b>Antipsychotics</b>			
Haloperidol	A	0.25–0.5	1.0–4.0
Pimozide	A	0.5–1	2–8
Risperidone	A	0.25–0.5	1–3.5
Fluphenazine	B	0.5–1.0	1.5–10
Tiapride	B	50–150	150–500
Ziprasidone	B	5–10	10–80



Categ A: 2 positive DBPC trials; Categ B: 1 positive DBPC trial

# $\alpha_2$ agonists

- Clonidine:
  - ✓ Activates presynaptic autoreceptors in locus ceruleus;
  - ✓ Begin at 0.05 mg/day with gradual increases on a TID/QID schedule;
  - ✓ Target dose of 0.2-0.3 mg/day recommended;
  - ✓ Major side effects: sedation and dry mouth, withdrawal hypertension
  - ✓ Clonidine patch: Smoother delivery; less withdrawal hypertension, TTS 1, 2 and 3 equals 0.1, 0.2 and 0.3 mg daily dose
- Guanfacine:
  - ✓ Less sedation compared to clonidine
  - ✓ Start at 0.5 mg at bedtime, gradually increasing doses given BID.
  - ✓ Target dose 1.5 to 4 mg/day; positive DBPC study in ADHD+Tics (Scahill et al, 2001)
  - ✓ Monitor BP & pulse, esp. early in treatment





# Antipsychotics in TD

- Long history of use in TD, effect sizes for treating tics at least 0.5
- Primarily help by blocking DA receptors → ↓ DA input from substantia nigra & ventral tegmentum to basal ganglia
- Typical: Haloperidol & Pimozide best studied, have DBPC trials (Sallee 1997)
- Atypical: Risperidone best studied (Shavitt 2006), one placebo controlled trial with Ziprasidone, case reports with Aripiprazole (Davies 2006, Bubl 2006); one case report found Clozapine ineffective in TD
- Watch for adverse effects including dystonias, metabolic syndrome and others. Get baseline weight, blood glucose, fasting lipid levels



# Risperidone vs. Clonidine

- 1 head-to-head trial Risperidone vs. Clonidine (Gaffney 2002) for children 7-14 yrs with TD: 8 wks trial
- Tics--Improvement 21 % Risperidone vs. 26 % Clonidine
- ADHD-- Responders 29% Risperidone vs. 50% clonidine
- OCD-- Responders 63% Risperidone vs. 33% clonidine
- Side effects: Subjects on clonidine had mild sedation, those in Risperidone group had 2 kg weight gain



# Recent data for Aripiprazole

- Murphy 2009: 6-week open-label trial: 8-17 years on average daily aripiprazole dose was 3.3 mg (range 1.25-7.5 mg): Significant pre-and post-treatment differences on Yale Global Tic Severity Scale motor, phonic & total tic scores.
- Budman 2008: Retrospective, observational study in 37 children and adolescents with Tourette's disorder refractory to previous treatment: Tics reduced with mean daily Aripiprazole dose 12.3 mg in 29 of 29 (100%) subjects; 8/37 (22%) subjects discontinued treatment; Most common adverse effects included weight gain, akathisia, and sedation.

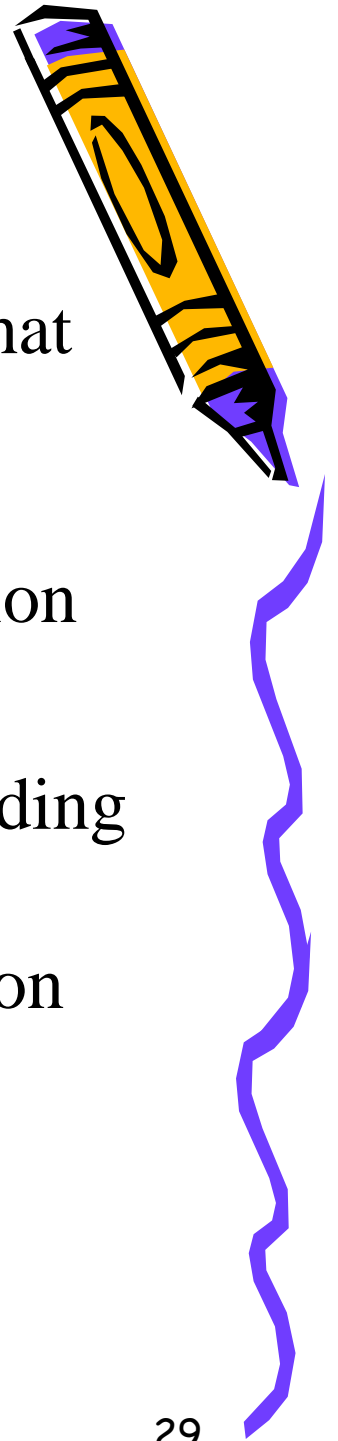


# Miscellaneous agents

- Pergolide (Gilbert 2003):
  - ❖ Mixed dopamine agonist used in Parkinson`s disease
  - ❖ When used in lower doses, possibly greater effect on presynaptic autoreceptors → decreased dopamine release
  - ❖ Evaluated in open-label and placebo-controlled trials → Positive but moderate effect on tics.
  - ❖ Adverse effects include nausea, syncope, sedation, and dizziness.
- Tetrabenazine:
  - ❖ Non-antipsychotic DA antagonist, approved as an investigational drug. Tetrabenazine may be useful, but more study needed
- Tianeptine: Recent European trial (Niederhofer, 2010)



# Miscellaneous agents



- Topiramate: Retrospective chart review suggests that topiramate can be used for tics in TS with at least moderate efficacy and adverse effects included cognitive/language problems (24.4%) and aggression or mood swings (9.8%) (Kuo 2010).
- Possible role for glutamate modulators in TS including glutamate's major role in cortico-striatal-thalamo-cortical circuits (CSTC), due to extensive interaction between glutamate and dopamine systems (Singer 2009).

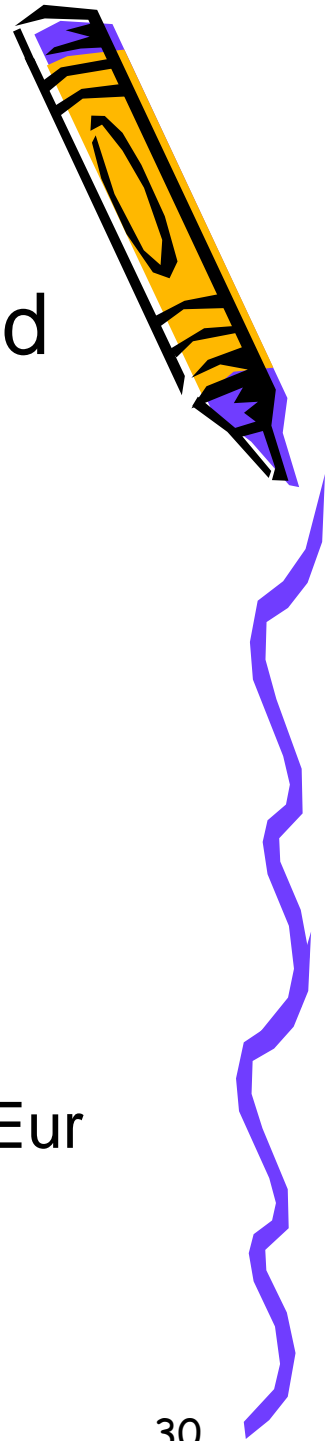


# Miscellaneous agents

Open label promising trials but double-blind trials not encouraging/inconclusive/not conducted:

- Levetiracetam
- Baclofen
- Clonazepam
- Talipexole

(European Clinical Guidelines for Tourette's syndrome. Eur Child Adolesc Psychiatry. 2011 April; 20(4): 173–196.





## Do children with no history of tics develop tics on psychostimulants more than placebo?

- N=416, 5 studies Concerta, MPH tid in DBPC trials for up to 2 years incidence of tics Concerta=4% MPH=2.3% and Placebo=3.7% ( Palumbo 2004)
- N=91, Placebo and MPH in children with ADHD w/o tics: 20% on MPH developed tics and 17% of those on placebo developed tics (Law and Schachar 1999)



# Do children with tics worsen with psychostimulant use?



- TACT study: n=136; 16 weeks
- 4-arm study of kids with chronic motor tics and ADHD: MPH, Clonidine, Clonidine+MPH, Placebo
- Overall severity of tics decreased in all active arms; best outcome with Clonidine +MPH
- Worsening of tics with agent: 1) Clonidine =26% 2) MPH= 20% and 3) Placebo = 22%
- Most children with chronic motor tics or TD treated with MPH tics will improve; about 20% may worsen





# Looking Beyond Psychopharmacology?

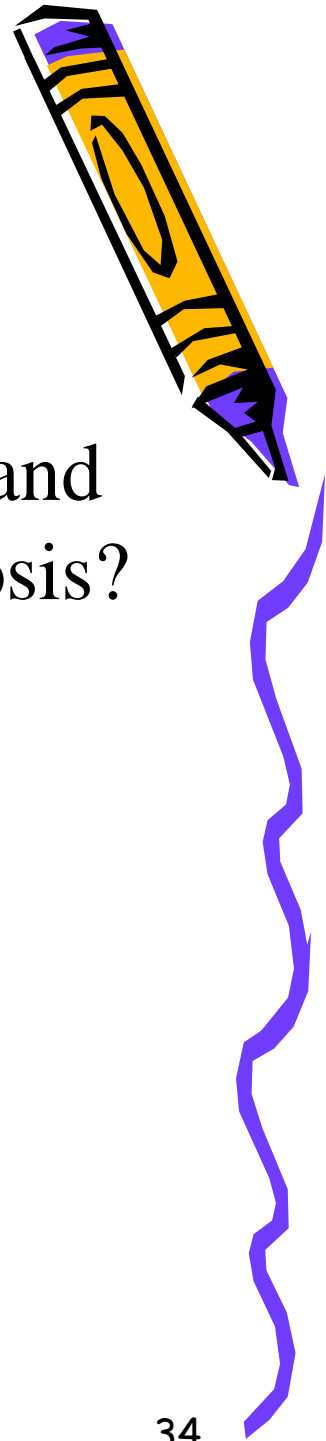
- Initial small case series on Deep Brain Stimulation (DBS).
- Pilot study from Japan: 3 cases with refractory Tourette's treated with DBS targeted at the centromedian-parafascicular complex-ventral oral thalamic nuclei of the bilateral thalami.
- Scores for the Yale Global Tic Severity Scale decreased from  $42.7 \pm 2.7$  (before DBS) to  $26.0 \pm 1.7$  (one year after DBS); increased patient satisfaction reported (Kaido et al. Neuromodulation 2011 Mar-Apr;14(2):123-8).



# Question 1

A 12 year old boy has phonic tics for 8 months and no motor tics. What is the appropriate diagnosis?

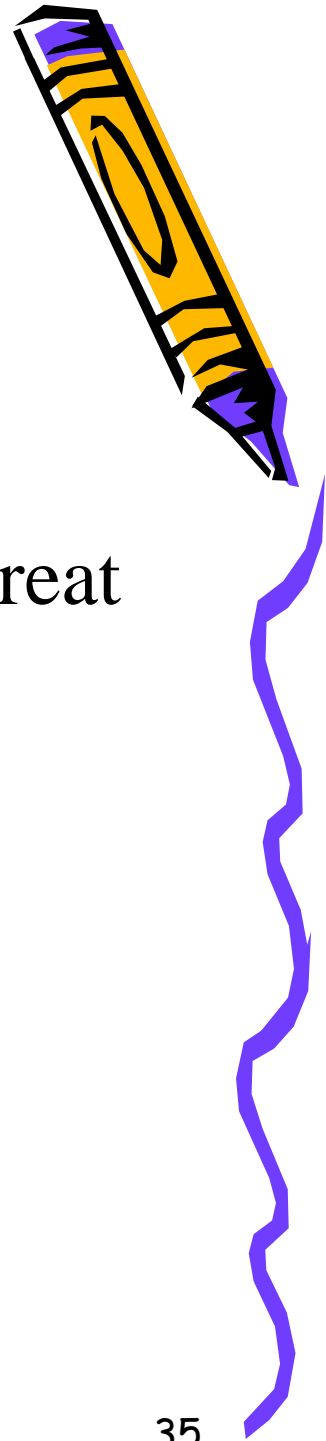
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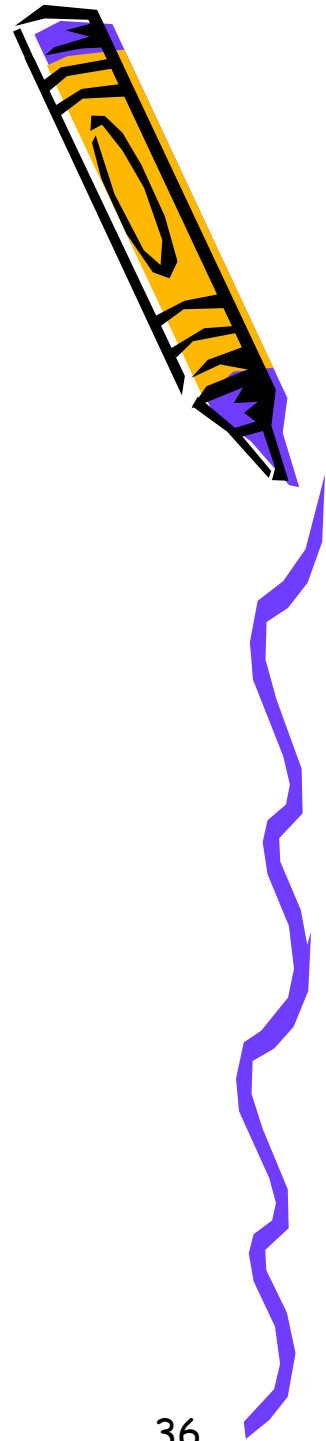
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- B) Guanfacine
- C) Atomoxetine
- D) Psychostimulants



# Question 3

The behavioral intervention that may have promising results for treating TD is:

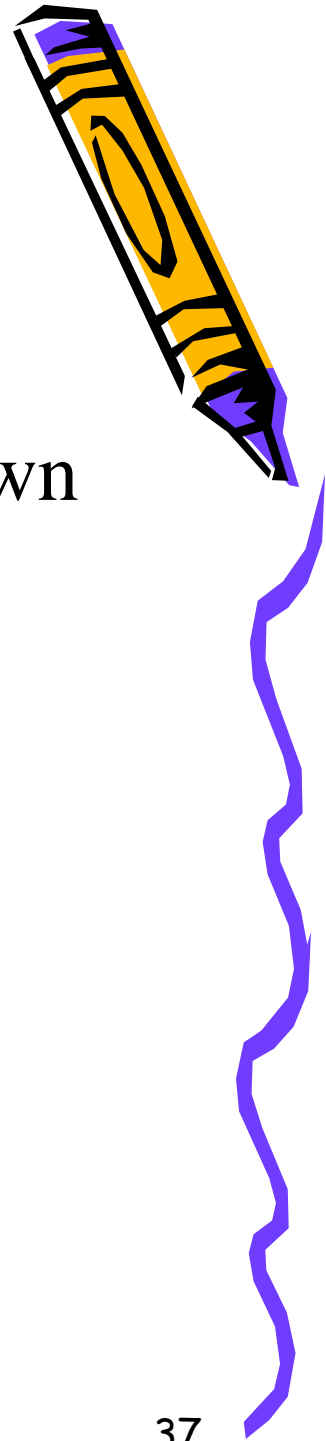
- A) Token Economy
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# Question 4

All of the following medications have been shown to be effective in reducing tics EXCEPT:

- A) Haloperidol
- B) Clozapine
- C) Clonidine
- D) Risperidone



# Question 5

Which of the following statements are true of TD?

- A) Coprolalia must be present to make a diagnosis
- B) Tics generally improve during adolescence
- C) Motor tics generally appear later than vocal tics
- D) A diagnosis of TD requires a symptom duration of 2 weeks



# Answers

- Question 1-B
- Question 2-D
- Question 3-B
- Question 4-B
- Question 5-B

