

MONITORING PSYCHIATRIC MEDICATIONS

Robert Hilt, MD

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Disclosures

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Partnership Access Line
Mental Health Consultation Outreach
for children

Topics Today

- SSRIs
- Stimulants
- Antipsychotics



Stimulants

A Case

- 8 year old girl
- Has always been “hyper” and “inattentive”
- Rating scales at home and school highly positive for ADHD symptoms
- You diagnose as ADHD, want to start a stimulant
- Mom is nervous about stimulant medications, says heard bad things about them
 - ▣ What do you tell her?

Common Stimulant Side Effects

- Decreased appetite, weight loss
- Nausea
- Insomnia
- Headaches
- Stomach aches
- Dry mouth
- Dizziness

- 30% don't respond/can't tolerate 1st trial
 - ▣ another stimulant helps over 1/2 of non-responders
 - ▣ 1st degree relative's response possibly predictive

Dealing With Common Side Effects

- *If* good response, often work around common side effects
 - ▣ Rebound—longer acting doses or small PM short acting?
 - ▣ Appetite suppression—big breakfast/dinner or weekend off? (if safe to do so)
 - ▣ Insomnia—change to wear off earlier, or treat?
 - ▣ Dysphoria, Irritability—change preparation?

Methylphenidate vs. Amphetamines

- May have different clinical responses, side effects
- Both will increase intrasynaptic dopamine and norepinephrine in the prefrontal cortex
 - ▣ Amphetamines increase dopamine a bit more than methylphenidate does
- Amphetamines can also increase intraneuronal serotonin

Stimulants and Tics

- Historical “contraindication” regarding use of stimulants in the presence of a tic disorder
- Sometimes tics worsen with stimulant
- on average children with both tics and ADHD who take a stimulant will show a *decrease* in their tics
- no longer considered by specialists to be a stimulant contraindication

Stimulants and Growth

- Decrease from projected normal weight gain is common
 - ▣ tends to resolve over time
 - ▣ increase caloric content of meals
 - ▣ drug “holidays,” big breakfast/dinner?
- Final adult height might be lowered by long term use of stimulants, by up to one inch (per some studies)
 - ▣ Alt. explanation is that ADHD → earlier growth in height
 - ▣ Other longitudinal studies have failed to find this association

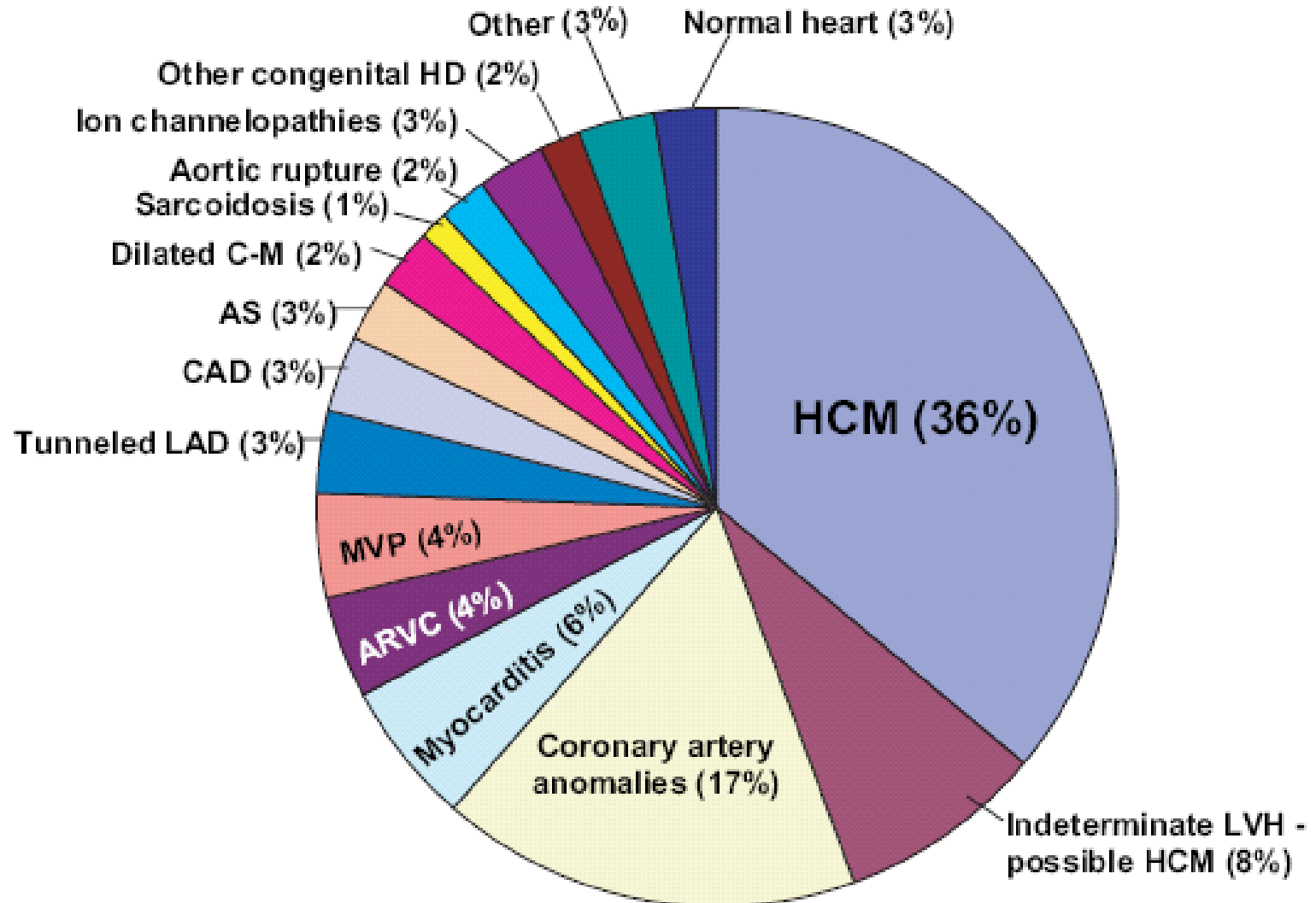
Stimulants and Drug Abuse

- **ADHD itself creates higher risk of substance use disorder (SUD)**
- No clear association between stimulant use and risk of SUD
 - ▣ Might even be protective for some
 - ▣ True ADHD patients typically report feeling “normal” when take med (not pleasure seeking)
- Stimulant diversion is commonplace
 - ▣ ~20% of high school kids have given their pills to others, usually family members

Stimulants and the Heart

- Facts about sudden cardiac death:
 - ▣ Sudden cardiac deaths in children are usually due to underlying heart defects
 - Hypertrophic heart, long QT, WPW, anomalous coronary artery, etc
 - ▣ Underlying heart defects are usually asymptomatic
 - ▣ Unexpected sudden cardiac deaths in kids are most likely to occur during strenuous exercise (↑↑pulse, BP)
 - ▣ **Stimulants are recognized to cause small increases in BP (2-4 mm Hg) and pulse (3-6 BPM)**
 - theoretically makes cardiac event during exercise more likely

Young Athlete Causes of SCD



PAL Conference October 8, 2011

Re 1435 young athlete deaths in 1980 to 2005, Maron BJ et al, 2007

Exercise is a Greater Risk than Stimulants

- Clearly the greatest risk agent for sudden death (in children with an unrecognized cardiac condition) is strenuous exercise
- No evidence that SCD risk is increased in children taking stimulants, beyond the risk of a child otherwise engaging in strenuous exercise

SCD Signal with Stimulants: Not Strong

- Total of 19 AERS reported sudden deaths in kids taking stimulants (12 amphetamine, 7 methylphenidate) over 5 years
 - ▣ Calculates to reported rate of <2 SCD per million children
 - ▣ Incomplete autopsy information in these events, but some discovered to have underlying heart defects
 - ▣ Base rate of SCD between 8 and 62 per million children in population
 - Rate of reported to unreported events is unknown

Utility of an ECG

- ECG can pick up asymptomatic HCM, long QT, WPW
- History and physical <10% sensitivity
- Fair evidence to say that if do anything to screen, an ECG would be the main test

Problems with ECG Screening

- SCD very rare, 1 in 200,000 high school athletes
- Very high false positive rates
 - ▣ 10-25% ECG false positives or pathologic sounding heart murmurs in adolescents overall
 - ▣ 10-40% ECG “abnormalities” in athletes

Why No Universal ECG Screens?

- AHA and AAP have decided universal ECG screening of athletes is not advised due to the problems with sensitivity and specificity
- No evidence that an ECG screen would reduce the risks of children taking stimulants any more than those not taking stimulants

Maron BJ 2007;

Josephine Ella MD, AACAP presentation Oct 30 2008

PAI Conference, October 8, 2011

Other ADHD Drugs

- Strattera not lower heart risk than stimulants
 - ▣ Also has noradrenergic stimulation
 - ▣ Label clearly warns of the same risks as stimulants

- Central alpha agonists (i.e. guanfacine, clonidine)
 - ▣ If underlying cardiac risk is for bradyarrhythmia (i.e. 3rd degree heart block), then meds are risky
 - ▣ Otherwise, are potentially a lower risk alternative

Stimulant Side Effects Summary

Common (>10%)	Less Common	Notable Rare Reactions (≤2%)
Decreased appetite	Irritability	Hallucinations
Nausea	Dysphoria	Mania
Weight loss	Cognitive dulling	Seizure
Insomnia	Obsessiveness	Loss of adult height potential
Headaches	Anxiety	Blood count suppression (MPH)
Stomach aches	Tics	
Dry mouth	Dizziness	
	Blood pressure/ pulse↑	

Stimulant Monitoring recommendation	Frequency Suggestion
Height and weight	At baseline and each follow-up, at least every 6 months
Blood pressure and pulse	At baseline and at least once on a given dose of medication
Cardiac history	At baseline to determine if any risks from adrenergic stimulation, ECG or refer if (+)
Refill monitoring	Track date of each refill to identify signs of drug diversion
CBC with Diff	For methylphenidate only, check once after 6 months of use (rare suppression from chronic use)
Determine if treatment response	Repeat ADHD specific rating scale(s) until remission is achieved. Increase at 2-4 week intervals if insufficient benefit.

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Selective Serotonin Reuptake Inhibitors (SSRIs)

A Case

- A 15 year old boy
- Has Major Depression, seeing a counselor
- Counselor sends him to see you, to request medication
- Still depressed, not making progress in therapy
- You decide to start fluoxetine
 - ▣ What do you say about side effect risks?
 - ▣ What needs to be monitored?
 - ▣ When do you see him back?

Many SSRI Choices

- SSRIs with 1 or more randomized controlled trial showing evidence of benefit IN CHILDREN for either depression or anxiety:
 - Fluoxetine (Prozac)
 - Sertraline (Zoloft)
 - Fluvoxamine (Luvox)
 - Citalopram (Celexa)
 - Escitalopram (Lexapro)

Common SSRI Risks (seen in >10%)

- Change in alertness (insomnia or sedation)
- Change in appetite (increase or decrease)
- GI symptoms (nausea, constipation, dry mouth)
- Restlessness
- Diaphoresis
- Headaches
- Sexual dysfunction

“Behavioral activation”

- SSRI risk in children at a rate of around 5%
- Is reversible with discontinuation
 - Impulsivity
 - Agitation
 - Irritability
 - Silliness
 - General hypomanic appearance
- Reaction usually independent of bipolar disorder

Rare SSRI Risks

i.e. <2% incidence

Serotonin Syndrome

- If overdose on SSRIs (not seen with usual doses)
- If SSRI combined with other serotonergic medication
 - MAOI
 - Other SSRIs
 - Triptans (rare)
 - Opiates (rare)
 - Stimulants (rare)

Serotonin Syndrome

- Cognitive: confusion, hallucination, agitation, hypomania, coma
- Autonomic: shivering, sweating, fever, diarrhea, nausea, increased pulse
- Somatic: hyperreflexia, myoclonus, tremor

- Treat by stopping drug, give support

Altered Platelet Function

- Increased bleeding time may happen with SSRI
 - Easy bruising
- SSRIs inhibit platelet reuptake of serotonin too
- Platelets use serotonin in their aggregation signaling

- Might be a caution for major surgery

Hyponatremia

- Seen in up to 2% of geriatric patients using SSRIs
- Unusual occurrence in non-geriatric patients
- Not something requiring active monitoring in kids

Prolonged QT interval

- Some recent reports of this with SSRIs
- Felt to be a very rare reaction
- SSRIs prospectively studied and given to post MI or other cardiac patients showed no induced risks or QT changes
- Not something requiring active monitoring in kids

SSRI Warning on Suicidality

- 2004: Black Box warning on antidepressant use in children, that they were associated with increased suicidality
- Not a new issue:
 - ▣ Reported since the 1960's that antidepressants could stimulate suicidality in some people during their early depression recovery

Why Did FDA Re-analyze trial data?

- Even in depression research, suicidality was often not specifically or prospectively studied
- “Emotional lability” vs. suicidality
 - ▣ To determine what “emotional lability” meant, had to go back to the original data sets

Result of the FDA-Columbia Review

- 24 studies with SSRI's submitted to FDA
 - 4582 children
- For all diagnoses: Suicidality OR **1.95**
(95%CI=1.28-2.98)
 - Statistic in the Black Box Warning
- For Major Depression: Suicidality OR **1.66**
(95%CI=1.02-2.68)
- No youth fatalities occurred in a clinical trial

Looking Below The Surface

- Anxiety studies raised the suicidality assessment of SSRI's

- Ascertainment bias: The 17 studies using any standardized question about suicidality showed slight decrease in suicidality on medication
 - ▣ OR **0.92** for worsening of SI on medicine (CI=0.76-1.11)
 - ▣ OR **0.93** for emergence of SI on medicine (CI=0.75-1.15)

SSRI Suicidality Differences

	Risk Ratio	95% confidence interval
▣ Venlafaxine	RR 8.8	(1.12-69.5)
▣ Sertraline	RR 2.2	(0.48-9.62)
▣ Paroxetine	RR 2.2	(0.71-6.52)
▣ Mirtazapine	RR 1.6	(0.06-38.37)
▣ Fluoxetine	RR 1.5	(0.74-3.16)
▣ Citalopram	RR 1.4	(0.53-3.50)

What Is Suicidality?

- Not all one thing
 - ▣ Thoughts of self harm
 - ▣ Thoughts of suicide
 - ▣ Making plans for committing suicide
 - ▣ Self harm actions (such as cutting)
 - ▣ Self harm actions with intent to die
 - Lethality/impulsivity of method is another factor
- Self-harm does not correlate well with suicidal behavior

Suicide Is Rare, Suicidality Is Common

- US suicide data:
 - ~2,000 completed suicides per year (up to age 19)
 - 500,000 adolescent attempts per year
 - 3rd leading cause of death in age 10-19
 - Males 370 attempts/completion
 - Females 3,600 attempts/completion
 - 17-19% of teenagers think about suicide in a given year
 - **8-10% of teenagers report making suicide attempts**
 - Rate of completed youth suicides of around 0.02%

Population Studies Say SSRI's Save Lives

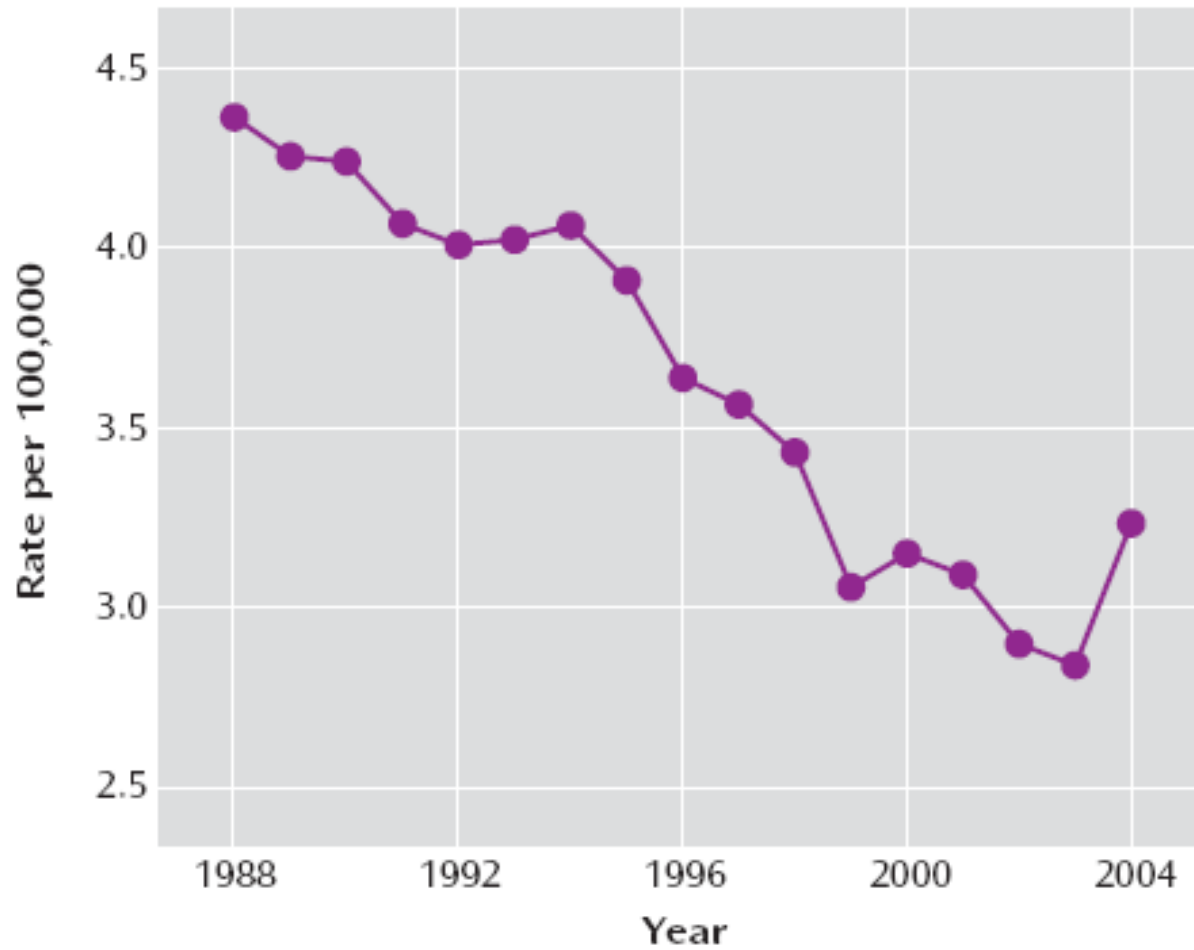
- In U.S. a regional 1% increase in adolescent use of antidepressants correlates with a decrease of 0.23 suicides per 100,000
- Population studies in Sweden, Italy, Netherlands, Australia, and U.S. all show decreased youth suicide rates with increasing antidepressant use
- 14% increase in U.S. youth suicides in 2004, the year SSRI usage started falling due to the black box warnings

Olson, M et al. Arch Gen Psych 2003

PAL Conference, October 8, 2011
Gibbons R et al. Arch Gen Psych 2004

Gibbons RD, Brown CH, et al 2007

FIGURE 2. Suicide Rate in Children and Adolescents (Ages 5–19 Years) in the United States, 1988–2004



My Understanding of SSRI Suicidality

- Agitation and “behavioral activation” long known to be SSRI effects for some who take them
- If you add agitation from SSRI to a significant mood/anxiety disorder, logical that some patients will get suicidal thoughts

How to Balance the Decision to Use SSRI's

- Recognize suicidal thoughts are common
- Completed suicide is very rare
- Depression and Anxiety can be serious problems
- Safety is important, but still unclear if and to what extent SSRI's are unsafe
- SSRI's do work for depression and anxiety in kids
 - ▣ Probably more reliable benefit the older the child

The SSRI Startup Discussion

- Discuss the suicidality warning
 - ▣ If new S.I. happens, stop med immediately
- Explain the more common side effects
 - ▣ Irritability, sleep changes, appetite changes, GI upset
- Note patients are last ones to recognize improvement
- Talk about follow up plan
 - ▣ phone or in person check in after 1-2 weeks screening for side effects, agitation, new suicidality
 - ▣ At appointment in 4-6 weeks decide what to do with dosage

SSRI Monitoring recommendation	Frequency Suggestion
Measure Height and weight	At baseline and each follow-up, at least every 6 months
Inquire about bleeding/bruising	At least once after initiation of medication
Inquire about activation symptoms	Screen for new irritability or agitation around week 2 & week 4-6
Inquire about new suicidal thoughts	Screen for suicidality around week 2, week 4-6, and other visits such as after dose increases
Determine if treatment response	Repeat disorder specific rating scale(s) until remission is achieved. Increase at 4-6 week intervals if insufficient benefit.

SSRI Side Effects Summary

Common (>10%)	Less Common	Notable Rare Reactions (≤2%)
Insomnia	Agitation	New Suicidality
Sedation	Restlessness	Serotonin syndrome
Appetite change (up ≈down)	Impulsivity	Easy bleeding
Nausea	Irritability	Hyponatremia
Dry mouth	Silliness	Mania
Headache	Constipation	Prolonged QT interval
Sexual dysfunction	Dizziness	
	Tremor	
	Diarrhea	

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Antipsychotics

A Case

- 12 year old boy with autism
- History of severe aggression and irritability
- Environmental measures are not helping
- You decide to try an atypical antipsychotic
 - ▣ What risks do you discuss with the parent?
 - ▣ What kind of monitoring would be required?

Common Side Effects

- Weight gain
- Muscle rigidity
- Parkinsonism
- Constipation
- Dry mouth
- Dizziness
- Somnolence/fatigue

Muscle Rigidity/Dystonia

- An early side effect
- Less common with atypicals than traditionals
- May decrease with continued use
- Acute dystonias are very distressing to patients
 - ▣ Specifically warn about this risk in advance
 - ▣ Explain the use of Benadryl
- ▣ Some prescribe anticholinergics right away to prevent this early reaction
 - Risk is how one reacts to anticholinergics

Weight Gain

- Two are reported as weight neutral in adults, but not reliably true in kids
 - ▣ Aripiprazole (Abilify)
 - ▣ Ziprasidone (Geodon)
- Worst weight gain occurs with olanzapine (Zyprexa)
- In general, kids gain on average more than 10 pounds over first 11 weeks of use
 - ▣ Refers to new use, not those who already gained weight
 - ▣ Wt. gain is often a reason for discontinuation

Metabolic Syndrome

- Abdominal obesity
- Glucose, lipid and cholesterol elevation
 - ▣ Check with fasting blood measurement
- Occasionally becomes a reason to stop medication
- Often correlated with weight gain, but not always

Sedation

- Can happen with all agents
- More prominent with olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal)
- Manage with night dosing

- NOT appropriate to use antipsychotics solely as a sleep aide

Tardive Dyskinesia

- choreiform and/or athetotic movements
- repetitively occur in skeletal muscles at rest
- can involve any voluntary muscle group (but most often peri-oral/lingual)
- potentially irreversible (less than 50% of cases spontaneously resolve within one year of onset)
- Increased risks from longer use, higher doses
- 5% chance per year typical antipsychotics
- 0.5% chance or less per year with atypicals

AIMS Exam

- Look for any movements while seated
- Open mouth and protrude tongue (twice)
- Tap fingers back and forth (watch face and legs)
- Check arms for stiffness/cogwheeling
- Observe standing with arms out, palms down
- Observe walking a few paces back and forth

- Goal to do this every 6 months

Neuroleptic Malignant Syndrome

- Rare allergic reaction
 - Typically happens early in treatment
 - high fever (i.e. 104-106° F)
 - muscle stiffness
 - autonomic instability
 - altered mental status
 - elevated CPK
-
- If new “flu” in first month of treatment, should see MD

Atypical Antipsychotics

Common (>10%)	Less Common	Notable Rare Reactions (≤2%)
<p>Weight gain</p> <p>Muscle rigidity</p> <p>Parkinsonism</p> <p>Constipation</p> <p>Dry mouth</p> <p>Dizziness</p> <p>Somnolence/fatigue</p>	<p>Tremors</p> <p>Nausea or abdominal pain</p> <p>Akathisia (restlessness)</p> <p>Headache</p> <p>Agitation</p> <p>Orthostasis</p> <p>Elevated glucose</p> <p>Elevated cholesterol/triglycerides</p>	<p>Tardive Dyskinesia</p> <p>Neuroleptic Malignant Syndrome</p> <p>Lowered blood cell counts</p> <p>Elevated liver enzymes</p> <p>Prolonged QT interval</p> <p>Tachycardia</p>

Atypical Antipsychotics

Monitoring recommendation	Frequency Suggestion
Height and weight	At baseline and at each follow-up (at least every 6 months)
Fasting blood sugar	At least every 6 months
Fasting triglyceride/cholesterol	At least every 6 months
Screen for movement disorder or tardive dyskinesia	At least every 6 months
CBC with Diff	Once to catch if any suppression, a few months after initiation
BP/Pulse	At least once after starting medication
Cardiac history	At baseline, get EKG if in doubt about risk from a mild QT increase
Determine if treatment response	Repeat disorder specific rating scale(s) until remission is achieved. Increase at 4-6 week intervals if insufficient benefit.

Questions?

Contact info:

www.palforkids.org

866-599-7257