Updates and Pearls in Pediatric Psychopharmacology for Primary Care Providers

+
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1

Questions

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2

Agenda

Review	Understand	Discuss	Review
•Review general principals and strategies when prescribing psychotropic medications to children and adolescents	•Understand when to start, stop, or adjust medications	•Discuss strategies for initial treatment of ADHD, anxiety and depression	•Review new medications in pediatric mental health

Discuss	Review	Discuss
•The role of a PCP in managing mood stabilizers and antipsychotics •How to manage medications after hospital discharge	•Review labs and tests that may be useful or necessary when managing psychotropic medications	•Discuss special considerations and cases

3

General Principals

+Clarify the diagnosis

+Rating scales are NOT diagnostic

+PHQ-9 score example

+Medications generally do not help situational symptoms

4

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

5

General Principals

+ Children take the same doses as adults for most medications
  + Medications are generally not weight dependent
+ Make only one change at a time!!
+ Monitor compliance
+ Know when to refer and who to refer to

6

General Principals

- Always define expectations of a medication before starting
- Treat with an adequate dose for an adequate time
- It is imperative that other resources are also being accessed
  - Therapy, exercise, sleep hygiene, management of family stresses, support at school
- Treating only with medications is almost never indicated

7

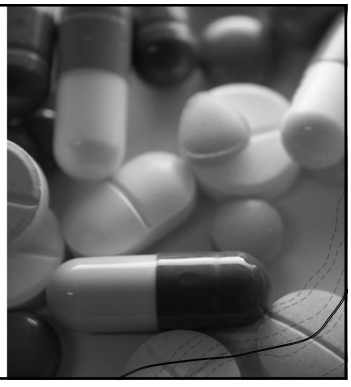
When to Start Medications

- Assess the level of functional impairment
  - Mild-moderate-severe
  - Mild impairment rarely justifies the use of medications
- Having a diagnosis does not require that medications be started
- Follow up depends on what medications you start and the severity of the symptoms, there is no set schedule

8

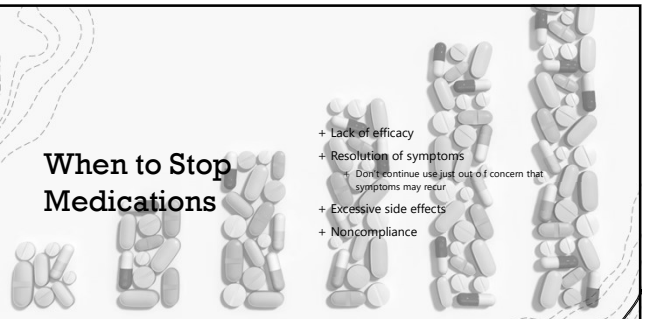
When to Change Medications or Doses

- Varies by medication class
  - Stimulants work right away so change can occur quickly
- If using antidepressants for anxiety or mood there should be some benefit within two weeks
  - Adjust dose at that time
  - Do not wait 4-6 weeks at a very low dose
  - If no response at all after 4 weeks and at least one dose increase has occurred consider changing medications



9

When to Stop Medications



- Lack of efficacy
- Resolution of symptoms
  - Don't continue use just out o f concern that symptoms may recur
- Excessive side effects
- Noncompliance

10

Let's Start with ADHD!

- Clarify the diagnosis
  - Are there psychosocial stresses
    - Food, housing, parenting
- Trauma may mimic ADHD symptoms
- Sleep disturbance
- Learning disorders or developmental delays

11

Epidemiology

+World wide prevalence is 5.3 %

+US prevalence for 4-17 year olds based on parent surveys is 7.2 % (current) and 9.5 % (ever)

+Studies vary on the estimate of persistent symptoms

- +35-80% of school age kids have symptoms into adolescence
- +50-65% of have symptoms into adulthood

12

ADHD

+A disorder of the ability to modulate and maintain ***appropriate*** attention for the task at hand, not a disorder of inattention

+Impulsivity and distractibility result from this inappropriate modulation
  +Lack of inhibition and focus

+Hyperactivity

13

Does the use of Medication for ADHD Impact Long Term Prognosis?

+ Studies generally conclude that psychosocial benefits occur
  + Improved employment, fewer MVA's, less SUD
+ Evidence for long term academic improvement is less compelling. Some studies show statistical improvement but it is small and likely clinically meaningless. Other studies show academic productivity improves but there is not improvement in ultimate academic achievement

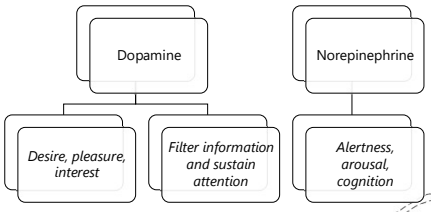
14

Symptomatic Versus Functional Improvements When Using Stimulants

+Relationship between symptomatic and functional improvement in remission in a treatment response to stimuli trial
  + Weiss et al, JACAP Vol 28, No 8 October 2018
  + 200 subjects with a mean age of 10.8 years completed an open label 11 week trial with extended release MPH
  + 57% who had symptom improvement also had functional improvement
  + 96% who had functional improvement also had symptom improvement
    + Weiss Functional Impairment Rating Scaled
      + Family, Learning, school behavior, life skills, self-concept, learning, school behavior, life skills, self-concept concert social activities, risky activities

15

Neurochemistry



16

The Effects of Long-Acting Stimulants and Nonstimulants

+The effects of long acting stimulant and non stimulant medications in children and adolescents with attention deficit hyperactivity disorder: a meta-analysis of randomized controlled trials
  +Carrillo-Urbana et al JCAP Vol 28. No. 28 October 2018
  +15 RTC's with 4648 subjects aged 6-17
    + Both drug classes showed benefit in total symptom reduction but stimulants had a greater benefit in subgroup scores
    + Primary treatment emergent side effects were decreased appetite for stimulants and somnolence for nonstimulants

17

How to Decide?

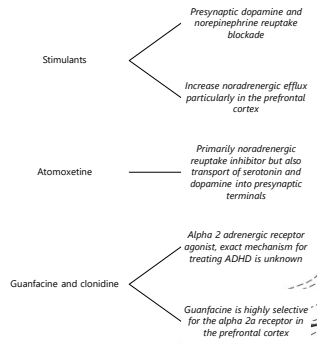
How do symptoms impact function throughout the day? Do you need relief all day?

Are there comorbidities to consider such as growth/appetite issues, anxiety, sleep problems, tics, substance use?

Will there be compliance issues with daily medications?

18

How do Medications Work?



19

Stimulants

+Pros
- +Work immediately so dose adjustment can occur quickly
- +Can be easily stopped and started
- +Come in long and short acting
- +Come in variety of forms: liquid, patch, pill, etc.

+Cons
- +May cause appetite suppression
- +May worsen tics
- +May cause sleep disturbance
- +Controlled substance
- +May be abused

20

Nonstimulants

Pros
- +Typically do not cause appetite suppression, changes in growth or significant sleep disturbance
- +Do not usually worsen anxiety
- +Not a controlled substance
- +Not abusable

+Cons
- +Take weeks to work
- +Must be taken every day
- +Cannot be easily started and stopped

21

Which Stimulant Should I Choose?

22

Taking a Wide Viewpoint

+Most persons with ADHD respond to any stimulant they take
- +They may have some tolerance differences

+All stimulants have efficacy for ADHD

+There are only two primary categories of stimulants
- +Methylphenidate products and amphetamine products

+All though there are lots of "new" ADHD stimulant medications they are all versions of the old ones

+New medications are costly and often not covered by insurance

23

Methylphenidate

+Pharmacokinetics
- +Onset in 30-45 minutes and mean duration of 3-4 hours for immediate release and up to 12 hours in ER formulations
- +Undergoes hydrolysis in the liver with little impact from metabolic enzymes
  - + D-methylphenidate is the active component and due to metabolic differences presynaptically is of higher concentration than l-methylphenidate
  - + Food does not impact bioavailability in any meaningful way

24

Amphetamine

+Pharmacokinetics
- +Onset of action in 30-45 minutes and mean duration of action 4-6 hours for IR and 8-12 hours of ER, 16 hours for Mydayis®
- +Metabolized by hydroxylation catalyze by CYP2D6 and oxidative deamination
  - + The impact of 2D6 variants is unclear because other metabolic pathways are also involved
- +Both the d and the l isomers are active
- +Food has little impact on bioavailability but acidic food may lower the absorption

25

Methylphenidate and Amphetamine

+Pharmacodynamics
- +Both inhibit DAT and NET transporters thus slowing reuptake in the synaptic cleft
- +Amphetamine is also transported into the presynaptic cell and displaces monoamines from storage creating an increase in the available monoamines to flow into the synaptic cleft.
- +Controversy exists about the impact of these differences

26

Practical Advice

Know	The mechanism of release • Multiphasic, short acting, continuous?
Know	The proportions • 50/50, 22/78, 30/70?
Know	The dose conversions • 2:1 methylphenidate to amphetamine

27

The Most Common Long Acting Stimulants

+Concerta®: methylphenidate , 8-10 hours, 22/78 immediate/continuous

+Metadate CD®, methylphenidate, 8 hours, 30/70, immediate/continuous

+Ritalin LA®, methylphenidate, 6-8 hours 50/50, biphasic

+Adderall XR®: MAS, 8-10 hours, 50/50, biphasic

+Vyvanse®: Dexedrine, 8-10 hours, continuous release

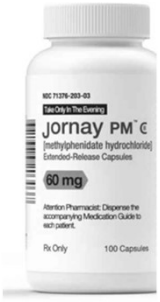
28

Jornay PM®

+Delayed release mechanism paired with an extended release mechanism

+Methylphenidate product

+Meant to be taken at night



29

Adzenys XR ODT®: amphetamine extended release dissolving tablet. Comes in a blister pack. 3.1 mg, 6.3, 9.4, 12.5, 15.7, 18.8. 18.8 mg is equivalent to 30 mg Adderall XR. Duration of 10-11 hours

Dynavel®: Extended releases liquid dexedrine. 2.5 mg amphetamine/ml, max dose of 20 mg

Aptensio XR®: Methylphenidate XR, one hour onset, 12 hour duration, may be sprinkled, 10-15-20-30-40-50-60 mg

Quillivant®: Extended release liquid methylphenidate

30

Evekeo®: short acting amphetamine, 5,10 mg tablets. 50% d-amphetamine and l-amphetamine. Adderall is 75%/25%

ProCentra®: a colorless bubble gum flavored short acting oral solution 5 ml/5mg dextroamphetamine

Mydayis®: 16 hour extended release mixed amphetamine salt

31

Stimulant Side Effects

Decreased appetite	**Wakefulness/Insomnia**	**Tics** • If pre-existing tics about 1/3 will get worse, 1/3 stay the same and 1/3 improve
Headache	**Slowed height velocity**	**Rebound irritability**

32

One Way

+Choose your methylphenidate or amphetamine product
- +Always start with long acting if possible
- +Increase dose after 3-4 days if no response to the first dose, increase again after 3-4 more days and then one more time if needed
- +If no response or negative side effects consider change to the other family
- +Repeat with second agent

+If side effects or no response after trying both families of stimulants consider nonstimulant

33

Special Consideration With Stimulants

Management of appetite suppression and/or weight loss	• Add an appetite enhancer such as mirtazapine
Managing sleep issues	• Add medication such as clonidine or go to a slightly shorter acting stimulant, for example Concerta® to Metadate CD®
Substance use concerns	• Switch to a non stimulant if needed
Rebound irritability	• Consider adding a short acting agent later in the day

34

Special Consideration With Stimulants

- Parents may not appreciate change if only giving meds at school
- Ok to give on weekends and days off if behavior warrants
- Only one consenting parent is needed in families whose parents are apart

35

Other Special Circumstances

+ Late onset ADHD?
  - + Girls may be diagnosed later
  - + Smart kids may go longer before the work is hard enough to challenge their focus and attention

36

Nonstimulants

+Noradrenergic
- +Atomoxetine
- +Viloxazine

+Alpha-Adrenergic
- +Clonidine
- +Guanfacine

37

Atomoxetine

- Atomoxetine target dose is about 1.4 mg/kg or a max dose of 100 mg
- Nausea and sedation are the most common side effects
- It take 6 or more weeks to fully work
- Not a controlled substance
- Does not work as an antidepressant
- Must be taken daily

38

The New Nonstimulant

+ Viloxazine (Qelbree®)
  - + Selective norepinephrine reuptake inhibitor
  - + Take up to 6 weeks to work but may start to have benefit in the first week
  - + Common side effects are fatigue, dry mouth, irritability, sleepiness, decreased appetite
  - + Start at 100 mg for 6-11 yrs old 200 mg for older kids. Max dose is 400 mg for kids. Approved in adults up to 600 mg
  - + May open up capsules to sprinkle

39

Alpha Adrenergics

+ Both clonidine and guanfacine come in long and short acting
+ Only guanfacine XR has FDA approval for adults
+ Sedation is the most common side effect
+ Take 4-6 weeks to work
+ Must be taken daily
+ Taper when discontinuing
+ Not a controlled substance

40

Alpha Adrenergics

- Start guanfacine IR at 0.5 mg twice daily and increase to 1 mg bid, then 1.5 mg bid and then 2 mg bid as clinically indicated.
- Start Guanfacine ER at 1mg at HS and increase every 5-7 days to a total of 4 mg
- Start Clonidine ER at 0.1 mg bid and increase as needed to 0.2 mg bid
- Clonidine IR needs tid dosing.

41

Special Considerations With Nonstimulants

- May not be a good choice for families that struggle with consistency in giving medications
- No value in stopping for the summer months since it takes 4-6 weeks to ramp back up
- Overall may have slightly less likelihood of working

42

Combinations

OK to use a stimulant with a nonstimulant

- Alpha-2 plus stimulant
- Atomoxetine plus a stimulant

Ok to use two nonstimulants

- Alpha -2 plus atomoxetine
- But likely little added benefit from using two non stimulants

43

Combined Stimulant and Guanfacine

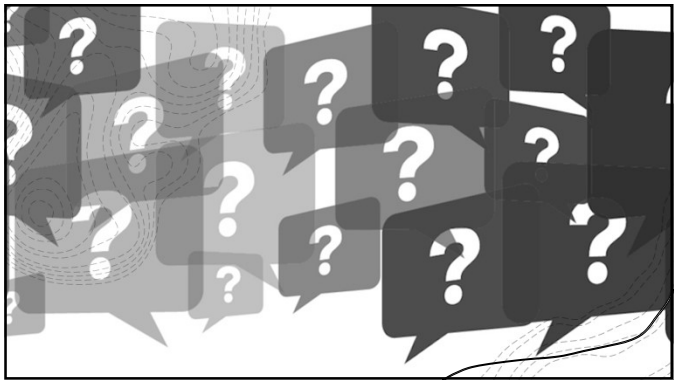
+Combined Stimulant and Guanfacine Administration in ADHD: A Controlled, Comparative Study

+JAACAP August 2016 McCracken et al

+8 week double blind randomized three arm study

+ Guanfacine1-3 mg, DMPH ER 5-20 mg daily, combination with flexible dosing
+ 207 subjects
+ Combination tx showed small but consistently greater reductions in inattention sub scales and overall benefit
+ No serious CV side effects, more sedation in the guanfacine groups

44



45

46

What is FDA approved for Mood and Anxiety

- Fluoxetine: MDD 8 and older, OCD 8 and older
- Duloxetine: GAD 7 and older
- Escitalopram: MDD 12 and older
- Anafranil: OCD 10 and older
- Fluvoxamine: OCD 8 and older
- Sertraline: OCD 6 and older

47

What are the New Medications for Depression?

+Vortioxitine (Trintellix)®

+Serotonin reuptake inhibitor and serotonin modulator, exact mechanism is not known
+Start at 10 mg, increase to 20 mg
+Metabolized by CYP2D6 (primary) and CYP3A4
+Common side effects of nausea, constipation, dry mouth, sexual dysfunction (potentially less than with other serontonergic agents)
+Two studies in children and adolescents have NOT shown efficacy

48

Vilazodone (Viibryd ®)

+Serotonin reuptake inhibitor and partial agonist

+Start with 10 mg and increase to a total of 40 mg, must be taken with food

+Side effects are diarrhea, vomiting, nausea, insomnia, dizziness, intense dreams

+Two studies done with kids/adolescents have shown no benefit in MDD

49

Esketamine (Sparvato ®)

Increases BDNF (brain derived neurotrophic factor)

Nasal spray infusion

Need two hours monitoring afterwards to assess HR and BP

May have immediate relief, twice weekly for a month then spaced out

Side effects of dizziness, sleepiness, anxiety, dissociation, increased BP

One month treatment $5-$7,000

One small case series of ketamine in 8 adolescents SC or IV showed benefit in depression

50

Brexipiprazole (Rexulti ®)

+Antipsychotic approved for augmentation of antidepressant in partially treated depression in adults

+Is FDA approved for ages 13 and older for children with schizophrenia but not FDA approved in this age for other uses

+Side effects are typical for antipsychotics

51

Dextromethorphan/Bupropion (Auvelity ®)

DXM is an NMDA receptor antagonist and sigma -1 agonist (both modulate glutamate transmission), bupropion increases the blood level of DXM through inhibition of CYP2D6

Side effects of dizziness, headache, diarrhea, dry mouth, sexual dysfunction, hyperhidrosis

Could not find studies in kids/adolescents

52

Gepirone ER (Exxua ®)

+Mechanism not clear but improves serotonin levels, partial agonist of 5-HT1A and 2A antagonist

+Side effects of dizziness, nausea, insomnia, stomach pain, indigestion

+Does NOT cause sexual dysfunction

+Extended release tabs 18.2-72.6 mg

+Not approved for kids, could not find controlled trials in kids

53

Levomilnacipram (Fetzima ®)

+Levomilnacipram is a serotonin and norepinephrine reuptake inhibitor

+Side effects include nausea, dizziness, sweating, constipation, insomnia, increased BP, sexual dysfunction

+CYP3A4 metabolized

+Not FDA approved

+2 studies in kids, not superior to placebo

54

Milnacipran (Salvella ®)

Not approved for depression but is approved for fibromyalgia

Selective serotonin and norepinephrine reuptake inhibitor

Not approved for use in kids/adolescents

55

Brexanolone (Zulresso ®)

FDA approved for post-partum depression

IV infusion in the hospital, One time infusion over 2.5 days

Increases GABA.

Side effects of extreme sleepiness, poor focus, dizziness

Cost of $30-$35,000

56

How to Proceed with Treatment?

+ Does the diagnosis matter?
  + Depression is an episodic illness, anxiety less so (exception may be OCD)
  + Diagnosis may impact prognosis
  + Diagnosis may impact therapy choices
    + For example ERP/CBT for OCD
+ Most of our common medications for children/adolescents depression also treat anxiety SSRI's, SNRI's
  + Exceptions may be mirtazapine and bupropion
+ Medications for anxiety may not treat ADHD
  + Buspirone, benzodiazepines

57

How to Proceed With Treatment

+ Medication treatment should not be initiated if therapy is not in place
  + Rare exceptions include illness so severe they cannot do therapy
  + Complete refusal to do therapy
  + Lack of resources to participate in therapy
    + Insurance, transportation, availability of a therapist

58

Treating Depression

+ Fluoxetine is FDA approve for 8-17
+ Escitalopram FDA approved for 12-17

59

Treatment of adolescent depression: TADS

+ Randomized controlled trial in 13 academic sites
+ 327 subjects between the ages of 12-17
+ Compared fluoxetine, CBT, and fluoxetine with CBT
  + CBT alone was less effective than combined treatment or fluoxetine and not significantly more effective than placebo at week 12
  + Combined treatment increased the speed of the response, quality of life, remission and overall safety, primarily by preventing treatment emergent suicidality
  + CBT benefit caught up with fluoxetine at week 18
  + All treatments were equally effective at 80% rate by week 36
  + The longer the treatment in TADS the more persistent the benefits over one year of naturalistic follow-up

60

Depression fundamentals

+If you have had one episode of depression the risk for recurrence is about 50%. After two episodes the recurrence risk rises to about 75%

+The average length of a depressive episode is about 6 months

+In most studies antidepressants work about 50-60% of the time

+Mood changes in younger patients may present as irritability and acting out more than "sadness"

61

Which medication to choose

+Consider family history of response and side effects to medications
  + Cytochrome P450 issues

+FDA approval

+Half life of the medication
  + Fluoxetine is the first choice if there is the likelihood of compliance issues

+Cost

+Tablets, capsules, liquid

62

Treating Depression

+First line treatment is generally considered to be an SSRI

+Treat with an adequate dose for an adequate time

+If no response after two weeks increase the dose.
  + For example: fluoxetine 20 to 30/40, sertraline 50 to 75/100

+If no response at 4 weeks and you have increased once then maximize dose and increase again

+At 4-6 weeks if no change consider a change in medications
  + Change to a second SSRI that has a different CYP450 metabolism

63

SSRI's pearls

+ All SSRI's have the same potential benefit and side effects
  + GI, restlessness, trouble with sleep, and sexual dysfunction are the most common
    + Talk about sexual dysfunction!!!!
  + Fluoxetine can be stopped without a taper due to long half life, all others need to be tapered
  + Fluoxetine and paroxetine are both P450 2D6 metabolized
    + Do not switch from fluoxetine to paroxetine or vice versa
  + If you start with fluoxetine switch to sertraline or citalopram
  + If you start with citalopram switch to sertraline or fluoxetine
  + If you start with sertraline switch to fluoxetine or citalopram

64

Treating Depression

After 2 SSRI's consider SNRI or bupropion

If there is a partial response augmentation could be considered

Add bupropion, 150 mg XL would be typical for augmentation

Do not augment if there was no response to the first medication

65

Tidbits about Specific Antidepressant Medications

Bupropion: Use the XL formulation, SR needs twice daily dosing and IR needs three times a day dosing

Venlafaxine: Use the XR formulation, IR needs twice daily dosing

All SSRI's and SNRI's should be tapered off to stop EXCEPT fluoxetine which can just be stopped completely all at once because of it's long half life

Mirtazapine: May cause significant weight gain and sedation.

66

How About Anxiety?

+Common childhood anxiety disorders
- +Separation anxiety
- +Phobia's
- +Selective mutism
- +Social anxiety disorder
- +Generalized anxiety disorder
- +OCD (no longer included under anxiety disorders in DSM-5)
- +Panic Disorder

67

Anxiety fundamentals

Younger children do not have the cognitive skills to discuss "worry"

Anxiety often shows up as physical symptoms such as headache or stomach ache and sleep disturbance

Anxiety disorders change with age and development
- Separation anxiety----- OCD/Social anxiety/GAD------ Panic disorder

Behavioral based therapies are crucial for the long term success in managing anxiety without medications

Benzodiazepines are rarely indicated for pediatric anxiety

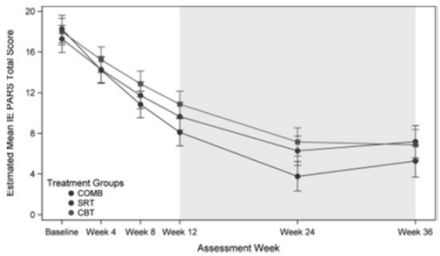
68

Treatment of adolescent anxiety (CAMS)

+Child and adolescent anxiety multimodal study
- +488 youth, 74% under the age of 12
- +Separation anxiety or Social anxiety
- +Randomized to 12 weeks of CBT, sertraline, combined therapy, or placebo
- +Responders attended six monthly boosters sessions
- +Assessment occurred at 24 and 36 weeks
  - + 80% of all responders maintained response

69

CAMS outcome



70

Remember

+Most medications for depression treat anxiety as well
- +May not be true for bupropion

+Some medications for anxiety may not treat depression
- +Buspirone
- +Benzodiazepines

71

First Choice

LIKE DEPRESSION FIRST CHOICE IS AN SSRI

ALL SSRI'S HAVE THE SAME POTENTIAL FOR BENEFIT FOR ALL ANXIETY DISORDERS

ALL SSRI'S HAVE THE RISK FOR SIDE EFFECTS

72

SSRI Side Effects

+GI upset: nausea, diarrhea
+Restlessness (akathisia)
+Disrupted sleep (start all SSRI's in the morning, if fatigue occurs switch to HS)
+May increase bleeding time
+Not usually responsible for significant weight gain
+May cause serotonin syndrome
  + Agitation, restlessness, diarrhea, tachycardia, elevated BP, fever, N and V, poor coordination, seizure

73

If SSRI's Do Not Work

+Consider trial of SNRI
+Buspirone for GAD
+Mirtazapine

74

Buspirone

+ Good for generalized anxiety but not for other forms of anxiety
+ Needs twice daily and sometimes three times daily dosing making compliance with an adolescent problematic
+ Common side effects: nausea, headache, mild fatigue
+ Easy to taper off if ineffective
+ Typical dose 20-60 mg in divided doses

75

Mirtazapine

+ Studies show benefit for social anxiety in peds as well as in reducing anxiety associated with ASD
+ Often useful as an added medication for persons with sleep issues or low appetite

76

Benzodiazepines

+One open label trial of alprazolam in12 youth with GAD, dose 0.5-1.5 mg/day. Significant improvement noted. Follow double blind study did not show benefit
+One clonazepam trial with 15 kids aged 7-13 with social anxiety or GAD had no benefit
+Consider use in responsible teens as needed for panic attacks
+PRN use common in the ASD/DD population but not for primary treatment of an anxiety disorder

77

Relationship	Inhibitory effect					Substrate				
	CYP 1A2	CYP 2C9	CYP 2C19	CYP 2D6	CYP 3A4	CYP 1A2	CYP 2C9	CYP 2C19	CYP 2D6	CYP 3A4
Antidepressants										
Agomelatine	0	0	0	0	0	**Yes**	Yes	Yes	No	No
Amitriptyline	0	0	+	+++	++	Yes	No	Yes	Yes	Yes
Duloxetine	0/+	++	0/+	0/+	0/+	**Yes**	No	No	Yes	No
Fluvoxamine	++++	+	++++	++	++	Yes	No	Yes	Yes	No
Fluoxetine	++/+++	+++	+	++	++	No	Yes	Yes	Yes	Yes
Mirtazapine	0	no data	no data	+	0	Yes	No	No	Yes	Yes
Moclobemide	0	+	0/+	+	0	No	No	Yes	No	No
Paroxetine	++	++	++	++++	++	No	No	No	**Yes**	**Yes**
Reboxetine	0	0	0	+	+	No	No	No	Yes	**Yes**
Sertraline	+	+	+	++	+	Yes	Yes	Yes	**Yes**	Yes
Venlafaxine	0	0	0	0	0	No	No	No	**Yes**	Yes
Vortioxetine	0	0	0	0	0	No	No	No	Yes	No

0 – no influence; + slight influence; ++ moderate influence; +++ strong influence; ++++ very strong inhibitory influence on isozymes CYP P450
The main enzyme responsible for metabolism is marked in bold.

78

	Pediatric			Adult			
	Starting dose (mg/d)	Typical dose range (mg/d)	FDA indications	Starting dose (mg/d)	Typical dose range (mg/d)	FDA indications	Half-life
Selective serotonin reuptake inhibitors							
Citalopram	10 to 20	20 to 40	–	20	40	MDD	20 hours
Escitalopram	5 to 10	10 to 40	MDD	10	20 to 40	MDD, GAD	27 to 32 hours
Fluoxetine	10 to 20	20 to 80	MDD, OCD	20	20 to 80	MDD, OCD, PD	4 to 6 days
Fluvoxamine	25 to 50	50 to 300	OCD	100 to 300	100 to 300	OCD	16 hours
Paroxetine	10 to 20	20 to 60	–	10 to 20	40 to 60	MDD, OCD, PTSD, GAD, SAD, PD	21 hours
Sertraline	25 to 50	100 to 200	OCD	50	150 to 250	MDD, OCD, PTSD, SAD, PD	26 hours
Serotonin-norepinephrine reuptake inhibitors							
Venlafaxine	37.5	150 to 225	–	37.5 to 75	75 to 375	MDD, GAD, SAD, PD	10 hours
Duloxetine	30	40 to 60	GAD	20 to 60	20 to 80	MDD, GAD	12.5 hours
Desvenlafaxine	25	25 to 100	–	50	50 to 400	MDD	11 hours
Atypical antidepressants							
Bupropion	100	150 to 300	–	100 to 150	150 to 300	MDD	21 hours
Mirtazapine	7.5 to 15	15 to 45	–	15	15 to 45	MDD	20 to 40 hours
Vilazodone	Not studied		–	10	10 to 40	MDD	25 hours
Vortioxetine	5	5 to 20	–	10	10 to 80	MDD	66 hours
Tricyclic antidepressants							
Clomipramine	25	50 to 200	OCD	25	100 to 250	OCD	32 hours
Desipramine	25 to 50	50 to 200	–	100 to 200	150 to 300	MDD	12 to 27 hours
Nortriptyline	30 to 50	30 to 150	–	100	75 to 150	MDD	18 to 44 hours

79

Comorbidity of ADHD and Depression/Anxiety

- OK to use stimulants plus SSRI
- OK to use alpha-2 agent and SSRI
- Strattera is 2D6 metabolized so avoid using with fluoxetine, paroxetine, bupropion and venlafaxine all of which require 2D6
- OK to use stimulant or alpha-2 agent with bupropion, mirtazapine, venlafaxine

80

What Do I Treat First, Depression/Anxiety or ADHD?

+ If planning to use a stimulant for the ADHD start that medication first
+ Reassess mood/anxiety after stable on stimulant
+ Are other medications still needed?
+ ARE appropriate nonpharmaceutical therapies in place?
+ Chicken and the egg
  + Is it truly inattention due to ADHD or inattention due to mood/anxiety?
  + Is depression/anxiety secondary to untreated ADHD?

81

And Finally…..

+ Mood stabilizers
+ Antipsychotics
+ Suggestions on handling those hospital discharge medications

82

Mood Stabilizers

+ This includes a wide range of medications
  + Divalproex sodium, lamotrigine, lithium
  + All antipsychotics
+ Almost all mood stabilizers will require some type of medical monitoring
+ Side effect profile tends to be harder to manage

83

What is the Evidence?

+ Lithium is FDA approved for ages 7 and older to treat bipolar disorder
+ Aripiprazole, risperidone, quetiapine approved for ages 10-17 for bipolar disorder
+ Olanzapine approved for 13 and older for bipolar disorder
+ Literature supports use in bipolar disorder

84

FDA Approved Uses for Newer Antipsychotics

Table B. Food and Drug Administration–approved second-generation antipsychotics

Generic Name	Indications	Age Group for Which Approved
Aripiprazole	Schizophrenia	Adults and adolescents (13–17 years)
	Bipolar disorder (manic/mixed) monotherapy or adjunctive to lithium or valproate	Adults and children (10–17 years)
	Adjunctive treatment of major depressive disorder	Adults
	Irritability Associated with autistic disorder	Children (6–17 years)
	Acute treatment of agitation	Adults
Asenapine	Acute schizophrenia	Adults
	Bipolar disorder type 1 (manic/mixed)	Adults
	Treatment resistant schizophrenia	
Clozapine	Reduce the risk of suicidal behavior in younger patients with schizophrenia	Adults
Iloperidone	Acute schizophrenia	Adults
Olanzapine	Schizophrenia	Adults and adolescents (13–17 years)
	Bipolar disorder (manic/mixed)	
	Bipolar disorder	Adults
	Treatment resistant depression	
	Agitation associated with schizophrenia and bipolar I mania	
Paliperidone	Schizophrenia	Adults
	Schizoaffective disorder	
Quetiapine	Schizophrenia	Adults and adolescents (13–17 years)
	Bipolar disorder (acute manic)	Adults, children, and adolescents (10–17 years)
	Bipolar disorder (depression)	
	Bipolar disorder (maintenance)	Adults
	Adjunctive therapy for major depressive disorder	
Risperidone	Schizophrenia	Adults and adolescents (13–17 years)
	Bipolar disorder (manic/mixed)	Adults and adolescents (10–17 years)
	Irritability associated with autism	Children (5–16 years)
Ziprasidone	Schizophrenia	Adults
	Bipolar disorder (manic/mixed)	
	Bipolar disorder (maintenance)	
	Acute agitation in patients with schizophrenia	

85

What is the Role of a PCP in Managing Mood Stabilizers and Antipsychotics?

+Should the PCP be starting these medications?
- +Comfort in making a diagnosis that requires these medications
  - + Bipolar disorder or psychotic disorder

+Level of crisis?
- +Acute/increased agitation in autism
  - + Starting antipsychotic may be necessary
- +Acute psychosis
  - + Should go to the ED

86

Mood Stabilizers

+Divalproex sodium
- + Labs needed: AST, ALT, platelets, blood drug levels
- + Comes in a wide range of forms, liquid, sprinkles, pills, ER tabs
- + Common side effects are GI, sedation, increased bleeding times

+Lithium
- + Labs needed: TSH, BMP (Cr), lithium levels
- + Comes in liquid, tabs and ER formulations
- + Common side effects are diarrhea, sedation, increased thirst and increased urination

+Lamotrigine
- + Must titrate very slowly due to risk of Steven's Johnson syndrome
- + No labs needed

87

Mood Stabilizers

+Antipsychotics
- +Significant side effects
  - + Increased appetite and weight gain
  - + Metabolic issues
    - + Must monitor lipids and HgbA1c
    - + Akathisia/restlessness
  - + Potential long term side effects
    - + Tardive dyskinesia
- +Typically would use second generation antipsychotics

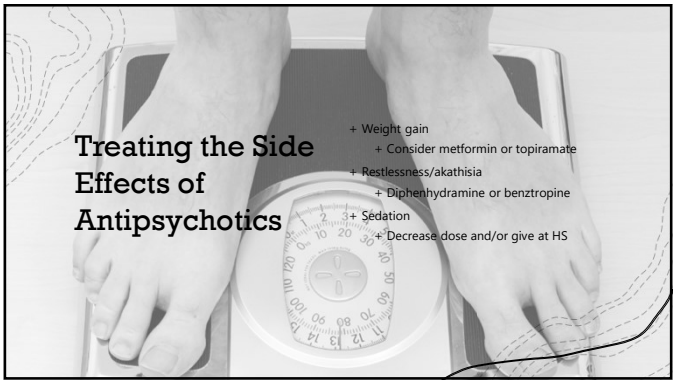
88

Antipscyhotics

+ Many uses for these medications
  - + Mood stabilization
  - + Psychosis
  - + Agitation
  - + Disruptive or aggressive behavior
  - + Self-injurious behavior
  - + Tics

89

Treating the Side Effects of Antipsychotics



+ Weight gain
  - + Consider metformin or topiramate
+ Restlessness/akathisia
  - + Diphenhydramine or benztropine
+ Sedation
  - + Decrease dose and/or give at HS

90

How About Sleep?

- Very young
  - Clonidine 0.05 mg-0.1 mg
  - Doxepin (comes in a liquid formulation)
    - Keep below 1 mg/kg
  - Mirtazapine
    - Smallest pill size is 7.5 mg also comes in a liquid formulation

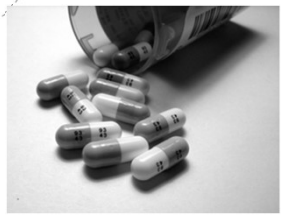
91

Other Sleep Options

- Trazodone
  - Smallest tablet is 50 mg, also comes in a liquid formulation
  - Higher doses generally not needed
- Hydroxyzine
  - Tabs and liquids
- Imipramine
  - Avoid higher doses, keep below 1mg/kg
- Antipsychotics can be considered if nothing else works
  - Quetiapine or olanzapine

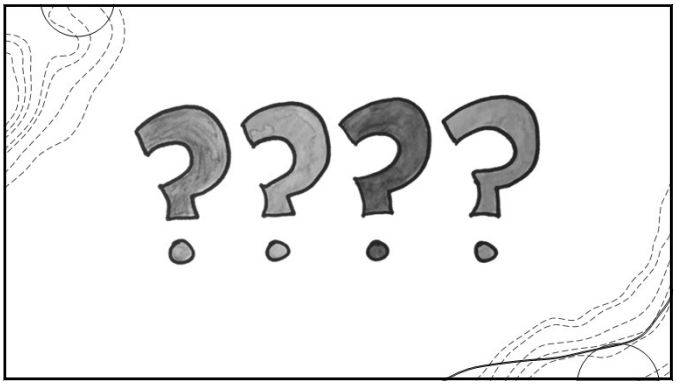
92

Hospital Discharge



- They are discharged on 5 medications and don't have a follow-up for 6 weeks!!!!!
  - Play is safe, don't make changes and just provide refills
  - Discuss questions with a colleague
- Do labs need to be obtained?
  - Drug levels?
    - Obtain a level about a week after recent dose changes. Patients are often discharged just after a change in dose with no updated levels at that dose

93



94