Reconnect & Rediscover:
A Convening Pediatric Experts and Advocates

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Psychotropic Medications for Children and Adolescents

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Disclosures

No relevant financial relationships to disclose

Off label prescribing: antidepressants and atypical antipsychotics

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Learning Objectives

- At the end of this session participants will be able to:
  - comprehend the basic mechanism of action of commonly used antidepressants and atypical antipsychotics
  - Understand pharmacogenetic influences observed in response to and adverse effects associated with commonly prescribed psychotropic medications
- At the end of this session participants will be familiar with issues around managing or co-managing children and adolescents on antidepressants and atypical antipsychotics

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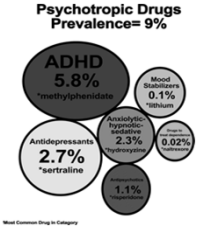
Psychotropic medication in children and adolescents in the US in 2014



Lopez-Leon, et al., 2018

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Prevalence of Psychotropic Use

- Insurance claim data of children/adolescents with ADHD – concomitant use of psychotropics with stimulants (Zhou et al, 2020)
  - 22.9% to 25.0% for children
  - 25.2% to 28.2% for adolescents
  - Most common SSRIs

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Trends In Prescribing

- Children on welfare are prescribed red-flag psychotropic medication at 2 to 3 times the rate of baseline (Ramen et al, 2021)
- Children on Medicaid experience polypharmacy (Davis et al, 2021)
  - Nearly all dx with disruptive behaviors (92% to 99%)
  - Polypharmacy: 26% on Medicaid and 34% in foster care
- Systematic review of system-wide interventions to improve antipsychotic treatment and management (Mackie et al, 2021)
  - Prior authorization programs demonstrate reductions in antipsychotic treatment or promotion of best practice parameters

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Washington Second Review

- A second review of children on 5 or more psychotropics in Washington State (Barclay et al, 2021)
  - Consultant advice fell into three categories: change, no change pending outcome of treatment adjustment, or no change
  - History of trauma prevalent
  - Increased psychosocial supports after reviews

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Guidelines Adherence

- Treatment utilization patterns by health insurance coverage (private and Medicaid) and age (Ali et al, 2019)
  - Psychiatric medication only was received:
    - 38% of preschool-aged children with Medicaid and 42% of those with private insurance
    - 43% of young children with Medicaid and 39% of those with private insurance
    - 55% of adolescents with Medicaid and 49% of those with private insurance

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Assessing Risk for Mental Health Disorders (GLAD-PC)

Recommendations (2018):

- Primary care clinicians are encouraged to seek training in depression assessment, identification, diagnosis and treatment (strong recommendation)
- Adolescent patients age 12 yrs and older should be screened annually for depression
- Patients with depression risk factors (such as history of previous episodes, family history, other psychiatric disorders, substance abuse, trauma, psychosocial adversity, etc.) should be identified and systematically monitored over time for the development of a depressive disorder
- PC clinicians should evaluate for depression in high-risk adolescents as well as those who present with emotional problems as the chief complaint.
- Assessment should include core symptoms of depression and functional impairment obtained from adolescents and family/caregiver separately

Zuckerbrot et al. (2018) GLAD-PC: Part 1 Practice preparation, identification, assessment and initial management. *Pediatrics, doi: https://d oi. org/ 10. 1542/ peds. 2017- 4081*

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USPSTF Screening for Depression

- Recommendation to screen all 12 to 18 year olds for depression
  - "Screening should be implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up."
- There is insufficient evidence regarding screening children 11 yrs or younger

U.S. Preventive Services Task Force, 2016

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Diagnosis of Depression

- Guidelines for Adolescent Depression in Primary Care (GLAD-PC)
  - Update in 2018
- Use a child/adolescent specific scale to evaluate
  - Children's Global Assessment Scale (C-GAS)
  - Columbia Depression Scale -Teen Version
  - PHQ-9: Modified for Teens

www.glad-pc.org

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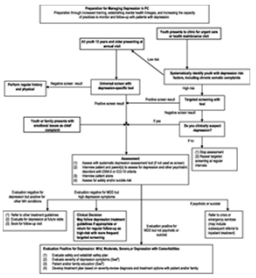
Clinical assessment flowchart.



Rachel A. Zuckerbrot et al. Pediatrics
doi:10.1542/peds.2017-4081

PEDIATRICS

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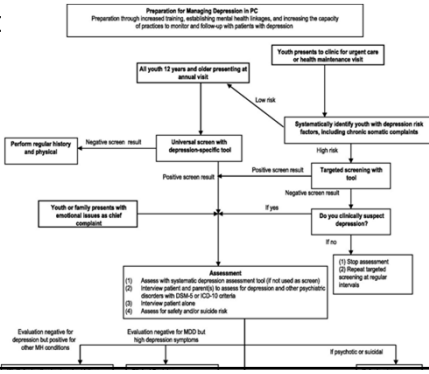
Assessment



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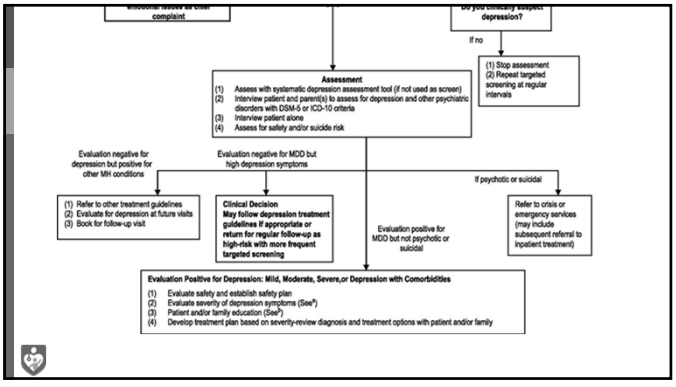

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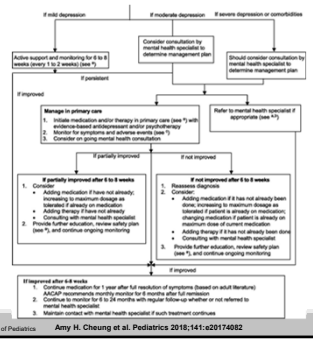
Clinical management flowchart



Amy H. Cheung et al. Pediatrics 2018;141:e20174082
PEDIATRICS

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Comparative efficacy and tolerability of antidepressants in children and adolescents

- A network meta-analysis through May 2015
- Included trials of amitriptyline, citalopram, clomipramine, desipramine, duloxetine, escitalopram, fluoxetine, imipramine, mirtazapine, nefazodone, nortriptyline, paroxetine, sertraline, and venlafaxine
- 5260 participants and 14 antidepressant treatments
- Only **fluoxetine** was statistically significantly more effective than placebo

Cipriani et al, 2016

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SSRI dosing and adverse effects

Table 2. SSRI Dosing and Adverse Effects

	Medication	Starting Dose*	Increments	Effective Dose	Maximum Dosage	Not to Be Used With	Common Adverse Effects	RCT Evidence for Efficacy
First Line	Fluoxetine	10 mg po qd	10-20 mg	20 mg	60 mg	MAOIs***	Headaches, GI upset, insomnia, agitation, anxiety	Y**
Second Line	Escitalopram (first-line: 12 and older)	5 mg po qd	5 mg	10-20 mg	20 mg	MAOIs***	Headaches, GI upset, insomnia	Y**
	Citalopram*	10 mg po qd	10 mg	20 mg	40 mg	MAOIs***	Headaches, GI upset, insomnia	Y
	Sertraline	25 mg po qd	12.5-25 mg	100 mg	200 mg	MAOIs***	Headaches, GI upset	Y

GLAD-PC.org, 2018

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SSRI Tapering/Switching Schedule

Table 3. SSRI Tapering/Switching Schedule

Medication	Tapering Increments	Time between each taper
Fluoxetine	10 mg	1-2 weeks
Sertraline	25 mg	1-2 weeks
Citalopram	10 mg	1-2 weeks
Escitalopram	5 mg	1-2 weeks
Fluvoxamine	50 mg	1-2 weeks
Paroxetine	5 mg	1-2 weeks

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ADRs of SSRIs in Children/Adolescents

- Decreased growth velocity
  - Fluoxetine (1.1 kg less, 1.1. cm less in ht)
- Behavioral disinhibition (more with preschoolers)
- Sedation
- Suicidality: increased risk until age 25 yrs

Safer, 2011

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Serotonin Syndrome

- A hyperserotonergic state that develops rapidly
  - with combined drug use of SSRIs and MAOIs, SSRIs and other serotonergic antidepressants, triptans for migraine, St John's Wort, dextromethorphan
- Complications include seizures, disseminated intravascular coagulation, respiratory failure, and hyperthermia
- If not adequately identified and controlled, can be fatal; mimics malignant hyperthermia and neuroleptic malignant syndrome

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Management Issues

- Accurate diagnosis of depression
  - Antidepressants for *major depression*
  - Bipolar ruled out
- Monitoring of symptoms and ADRs
- Drug Interactions
- Lifestyle modifications

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Long-term Management

- Maintaining Medication
  - Continue for 6-12 months following cessation of symptoms. Some may need 2 or more years of maintenance to prevent relapse.
  - Once stabilized, follow-up monthly
  - Evaluate target symptoms, adverse reactions & medication compliance at each visit
  - Obtain adolescent and parent symptom checklists every 3 months.
- Stopping Medication
  - Taper slowly

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Resources for Practice

- GLAD-PC Toolkit
  - General psychosocial screens
    - Whole Child Assessment (WCA)
    - Strengths and Difficulties Questionnaire (SDQ)
    - Pediatric Symptom Checklist-17 (PSC-17, parent and youth versions)
  - Adolescent depression screening tools
    - PHQ-9 in multiple languages
  - Prescribing guidelines
  - Speaking with adolescents and parents
  - Educational materials for adolescents
  - www.glad-pc.org

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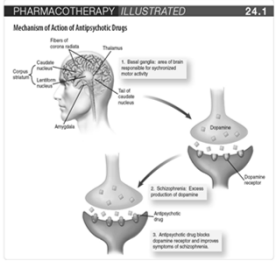
Atypical Antipsychotics

- Used to treat Tourette syndrome and behavioral symptoms associated with autistic disorder, childhood schizophrenia, and bipolar disorder
- Mechanism of Action
  - Combination of partial agonist activity at dopamine type 2 (D2 and D3) and serotonin type 2 (5-HT1A) receptors and antagonist activity at 5-HT2A receptors



Adams & Koch, 2020

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ADRs of Antipsychotics in Children and Adolescents

- Sedation
- Extrapyramidal symptoms (EPS)
  - Aripiprazole 25% EPS in 13 to 17 yr olds (13% in adults)
- Drooling
- Weight gain
  - olanzapine – risk of weight and hyperlipidemia gain higher in children than adults
  - Risperdone – 14% of adolescents gained average 9 kg (20 lbs)
- Metabolic and lab changes
- Neuroleptic Malignant Syndrome
- Hypertension (quetiapine – risk higher in peds pts)
- Prolonged QT
  - Quetiapine
  - Ziprasidone

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Metabolic and lab changes

- Increases in fasting insulin, insulin resistance, fasting glucose, leptin, triglycerides
- Decreased HDL levels
- Elevated prolactin levels
- Elevated liver enzymes

- Metabolic monitoring low among PSY and PCP prescribers (Wakefield et al, 2019)
  - BMI measured by both
  - Glucose and lipids had low monitoring rate

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Neuroleptic Malignant Syndrome (NMS)

- Potentially fatal adverse reaction
- Symptoms include altered mental satus (61%), high fever (78%), diaphoresis, muscle rigidity (70%), tachycardia (74%), BP fluctuations
  - Elevated creatine phosphokinase in 100%
- Without quick, aggressive treatment condition can deteriorate to stupor or coma
- Treatment includes antipyretics, electrolytes, muscle relaxants

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Atypical Antipsychotic Co-management Issues

- Appropriate referral and diagnosis
  - collaboration with a psychiatrist or an advanced practice psychiatric/mental health nurse is essential for quality care
- Monitoring
  - Weight, lipids, glucose
  - Liver function
  - EPS or NMS symptoms
  - Suicidal thoughts
  - Behavior

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Sleep Disorders

- CBT or pharmacotherapy
- Melatonin
  - Onset 30 to 60 min
  - 1 to 3 mg before bed
  - No well controlled studies, no long-term studies
  - ASD quicker sleep onset and improved night wakening
- Melatonin agonists
  - Ramelteon binds to the melatonin MT1 receptor
  - Not approved for children or adolescents

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Sleep Disorders

- Antihistamines
  - OTC diphenhydramine
  - dose 1 mg/kg up to 50 mg/d
  - Children may have paradoxical reaction
  - No change in nighttime wakening's when compared to placebo
- Benzodiazepine-like drugs
  - Zolpidem, zaleplon, eszopiclone
  - Not approved for use in children
  - Studied for
- Alpha agonists (clonidine) in children with ADHD
  - Improved sleep latency (Bruni et al, 2018)

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Practice guideline: Treatment for insomnia in children and adolescents with ASD

- American Academy of Neurology (Buckley et al, 2020)
- Recommendations
  1. Address coexisting medical conditions
  2. Behavioral strategies
  3. Melatonin – medical grade (2 to 10 mg)
  4. CAM approaches – no high-quality evidence

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Pharmacogenomics of psychotropics

- Dopamine transporter gene (DAT1) may cause lower response to methylphenidate
- Amoxetine is metabolized by CYP2D6 and CYP 3A4
  - 5-10% of caucasians and 0-19% of African Americans are slow metabolizers due to 2D6
  - May be related to poor response and increase risk for ADRs
- Poor or ultrarapid metabolizers of 2D6 may have altered response to antidepressant medications

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Pharmacogenomics

- Individual responses to medication therapy may occur
- When to consider pharmacogenetic testing
  - When not responding and compliance is assured
  - Especially if two failed medications
  - Significant side effects
- Genomind Assay is covered by Medicaid
  - 24 genes

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Pharmacogenomic Testing Policy Statements

- The American Academy of Child and Adolescent Psychiatry (2020) recommends:
  - Clinicians avoid using pharmacogenetic testing to select psychotropic medications in children and adolescents.
  - Future high-quality prospective studies to assess the clinical significance of pharmacodynamic and combinatorial pharmacogenomic testing in children and adolescents.
- American Academy of Child and Adolescent Psychiatry (Ramsey et al, 2021)
  - pharmacogenetic testing may inform dosing for antidepressants that are commonly used in child and adolescent psychiatry
  - dosing recommendations or assessment of risk for severe hypersensitivity reactions are based on pharmacogenetics in the Food and Drug Administration (FDA)-approved product inserts

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Summary

1. Antidepressants can be safely prescribed, BUT
   - Require close monitoring
   - Combine with CBT if possible
2. Atypical antipsychotic prescribing requires:
   - Accurate diagnosis by clinical expert
   - Close monitoring for ADRs
3. Consider pharmacogenetics if not getting expected response

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Questions?

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