The Use of Psychotropics in the Pediatric Population
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Objectives
- Define psychotropics and discuss the different classes used in pediatrics
- Discuss barriers for the effective use of psychotropics in the pediatric population
- Understand the role that psychotropics play in the treatment of varying mental disorders in the pediatric population
- Review the most commonly used psychotropics in pediatrics
- Describe important side effects and monitoring parameters for psychotropics used in the pediatric population

Introduction
- Psychotropic: a chemical substance that changes brain function and results in alteration of perception, mood, or consciousness
- Psychotropic Classes Utilized:
  - Antipsychotics
  - Antidepressants
  - Benzodiazepines
  - Anticonvulsants
  - Hypnotics
  - Stimulants
Barriers in Pediatric Psychopharmacology

- Limited research on existing medications for new indications
- Lack of adequately trained workforce
- Consent
  - Sets of knowledge and attitudes about medications
  - Competent to make the decision?
  - Understanding changes with age
- Compliance
  - Network
  - Attitude
  - Ability to swallow
  - Taste of the medication
  - Adverse effects

Place of Medication in Therapeutic Planning

- Targets of Medication need to be:
  - Clear enough to allow monitoring
  - Practical enough to change
  - Simple enough for explanation
- Targets:
  - Symptoms
  - Course of a condition
Place of Medication in Therapeutic Planning

- Pharmacological versus Psychological interventions
  - Advise patients on the best treatment for **them**
  - Medication is **not** always a last resort
  - Initial treatment based on each case
  - Choice of intervention is **not** due to cause

Mental Illnesses in Pediatrics

- Attention Deficit Hyperactivity Disorder (ADHD): 8.4%
- Anxiety: 4.7%
- Behavioral or conduct problems: 4.6%
- Depression: 3.9%
- Bipolar Disorder: 1.8%
- Autism Spectrum Disorder: 1.1%
- Tourette's Syndrome: 0.3%
- Schizophrenia: 0.23%
- Substance Use Disorder
  - Alcohol: 4.2%
  - Illicit drug: 4.7%
  - Cigarette 2.8%

SCHIZOPHRENIA
Schizophrenia

- General principles:
  - Antipsychotic drug regimens are the cornerstone
  - Require pharmacotherapy, family and individual counseling
- Antipsychotics
  - Safety and efficacy based on adult trials
  - Young show greater sensitivity to adverse events

Antipsychotics

- Recent randomized control trials on:
  - Risperidone, olanzapine, aripiprazole, paliperidone
- Choice of antipsychotic determined primarily by side effect profile
  - Atypicals preferred in young and treatment naïve
- Start below the usual range for adults and titrate slowly upwards to minimum effective dose

Antipsychotics

- First-Generation (aka typical):
  - Haloperidol (Haldol): ≥3 years
  - Trifluoperazine (Stelazine): ≥6 years
  - Thiothixene (Navane): ≥12 years
- Second-Generation (aka atypical):
  - Risperidone (Risperdal): ≥13 years
  - Olanzapine (Zyprexa): ≥13 years
  - Quetiapine (Seroquel): ≥13 years
  - Aripiprazole (Abilify): ≥13 years
  - Paliperidone (Invega): ≥12 years
Schizophrenia: Recommended order of treatment

- Atypical
  - No response/intolerable
  - Different atypical or typical
  - Continue for 2 years
  - Clozapine

Antipsychotics: Adverse Events

First-Generation
- Extrapyramidal motor symptoms (EPS)
  - Dystonia
  - Parkinsonism
  - Akathesia
  - Tardive Dyskinesia

Second-Generation
- Obesity
- ↑ triglycerides
- ↑ Nonhigh-density lipoproteins
- ↑ Cholesterol
- ↑ Glucose
- Diabetes II
- Hyperprolactinemia

Antipsychotics: Adverse Events

- Weight gain
  - Greatest with Olanzapine
  - Least with aripiprazole

- EPS
  - Greater with typicals (eg: haloperidol) and higher doses of risperidone
  - Aripiprazole: akathisia
Antipsychotics: Adverse Events

- Sedation
  - Greater with olanzapine, clozapine, quetiapine and haloperidol than with risperidone and aripiprazole

- Hyperprolactinaemia
  - Greatest with risperidone and haloperidol
  - Least with quetiapine and aripiprazole

Antipsychotics: Monitoring

- Baseline Monitoring
  - Physical examination
    - Height & weight (BMI)
    - CV exam: pulse & BP
    - Neurological exam: evidence of abnormal movement
  - Labs:
    - CBC, LFTs, BMP, prolactin, fasting BG, HbA_1c, plasma lipids

- Monitoring while on treatment
  - Weight:
    - Weekly 1st 6 wks
    - At 12 wks
    - Every 6 months thereafter
  - Pulse, BP, prolactin, fasting BG, HbA_1c, lipids
    - At 12 wks
    - Every 6 months thereafter
BIPOLAR DISORDER

Bipolar Disorder

- General Approaches
  - Focus treatment on most disabling aspects
  - Later treatment can address other issues
  - Must consider common issues affecting children and adolescents, such as substance abuse and pregnancy
  - Comprehensive treatment requires both psychotherapy and psychopharmacology
  - Treatment must address the phase of the illness

Step 1: Initiate antimanic agent

1st-line: lithium, valproate, carbamazepine, risperidone, olanzapine, quetiapine

Full Response:
- Continue maintenance treatment (with side effect monitoring)
- Proceed to Step 2

Partial Response:
- Consider augmentation with second antimanic agent
- Consider how associated/comorbid conditions are affecting response

Non Response or not tolerated:
- Switch to other antimanic agent
Bipolar Disorder: Mania

- Current available antimanic medications:
  - Second-generation antipsychotics (SGA)
  - Lithium
  - Antiepileptic drugs (AED)

- Recent RCT support the following:
  - SGA are effective and potentially superior
  - Lithium’s role in pediatric BD is less clear
  - AED may be less efficacious

Bipolar Disorder: Mania

- SGA
  - Strongest efficacy data
  - FDA-indications to treat mania or mixed states in 10-17 years:
    - Risperidone, aripiprazole, quetiapine, asenapine

- Lithium
  - Mixed support for efficacy
  - FDA-indicated to treat mania in 12 years and older

Lithium: Adverse Events

- Adverse Events:
  - Early: fine tremor, polydipsia, polyuria, nausea, malaise, weight gain, headache, diarrhea
  - Late: continued hand tremor that may worsen, polydipsia, polyuria, weight gain and edema, thyroid and renal abnormalities, dermatologic abnormalities, fatigue, leukocytosis
**Lithium: Adverse Events**

- **Toxicity:**
  - Diarrhea, vomiting, mild ataxia, coarse hand tremor, muscular weakness and fasciculations, drowsiness, sedation, slurred speech, and impaired coordination
  - Life-threatening toxic effects: cardiac arrhythmias and severe central nervous system difficulties

**Lithium: Monitoring**

- **Serum Lithium Concentrations:**
  - Every 3-4 days during initiation
  - 1-2 months once stabilized
  - Obtain 8-12 hours post-dose
  - Reference Range:
    - Acute mania: 0.6-1.2 mEq/L
    - Maintenance: 0.8-1 mEq/L
    - Toxic: > 1.5 mEq/L

- **Baseline:**
  - CBC, urine analysis, pregnancy test, thyroid function tests, ECG
  - Serum Na, calcium, creatinine, BUN
  - EEG in children with seizures or known abnormalities in EEG

- **Periodic Monitoring:** thyroid, kidney, and cardiac function
Bipolar Disorder: Mania

- AED:
  - Weak evidence of efficacy
  - Benefits seen in small open-label trials with carbamazepine, valproate, and lamotrigine
  - No placebo control group
  - Safety data is stronger

Antiepileptics

- Valproic acid
  - Boxed Warnings:
    - Hepatotoxicity and pancreatitis
      - More common in < 2 years old
    - Mitochondrial disease
    - Teratogenic
  - Adverse effects:
    - Transient: nausea, vomiting, indigestion
    - Psychiatric effects: emotional upset, depression, psychosis, aggression, hyperactivity, behavioral deterioration
    - Thrombocytopenia
    - Polycystic ovary syndrome

Antiepileptics

- Valproic acid
  - Monitoring:
    - Liver enzymes
      - Especially during 1st 6 months
    - CBC with platelets
      - Prior to initiation and periodically
    - Serum concentrations
      - Trough: 50-125 mcg/mL
Antiepileptics

- Carbamazepine
  - Boxed Warnings
    - Aplastic anemia/agranulocytosis
      - Very rare
    - Serious dermatologic reactions
      - SJS/TEN
      - HLA-B*1502 allele
    - Adverse Effects: dizziness, drowsiness, unsteadiness, nausea, vomiting
  - Monitoring:
    - CBC with diff, LDL, LFTs, TSH, BUN, serum Na
    - Serum levels: 4-12 mcg/mL

Antiepileptics

- Lamotrigine
  - Boxed Warning: Serious skin rashes
    - SJS/TEN
    - Increased risk with age <12 or co-administration of valproic acid
  - Monitor:
    - CBC with diff, kidney and liver function, hypersensitivity reactions

Bipolar Disorder: Depression

- Lack of RCT to guide medication treatment of depression and anxiety in BD
- Data suggests that:
  - Youth spend considerable time struggling with depression
  - Youth often receive SSRIs with no induction to mania
  - Risk of antidepressant-induced mania higher in prepubertal children
Depression

Type and intensity of treatment depends on severity

- Mild: assessment and education
- Moderate:
  - NICE guidelines: CBT, IPT, or family therapy first; then add medication if no response
  - Never use antidepressants without psychotherapy
- AACAP guidelines:
  - Combination therapy preferable
  - Monotherapy acceptable in certain cases
- Persistent or Severe:
  - SSRIs, CBT, IPT, or combination

Progress should be reassessed in 4-6 weeks

Tricyclic antidepressants:
- Not efficacious

Selective Serotonin Reuptake Inhibitors:
- Fluoxetine (Prozac): first-line
  - Only agent recommended for use in adolescents by NICE guidelines
  - FDA-approved for both preadolescent and adolescent depression (≥ 8 years)
Selective Serotonin Reuptake Inhibitors:
- Escitalopram (Lexapro):
  - FDA-approved for depression in 12-17 years
- Sertraline (Zoloft):
  - Has been reported superior to placebo
  - Not FDA approved for pediatric depression
- Citalopram (Celexa):
  - Found to be as efficacious as fluoxetine
  - Not FDA approved for pediatric depression
- Paroxetine (Paxil):
  - Not recommended

SSRIs: Adverse Effects & Monitoring
- Headache, N/V, diarrhea, sleep disturbance, weight gain/loss, anxiety, SIADH
- Behavioral disinhibition
- Sexual dysfunction
- Serotonin Syndrome
- Discontinuation syndrome

SSRIs: Adverse Effects & Monitoring
- Suicidal ideation
  - Incidence is rare
  - Studies have shown attempts more common prior to initiation of SSRI
  - Occurs within first 3-5 wks
  - Combination of meds and therapy needed
- Monitoring: weight, CBC, LFTs, Electrolytes, suicidality
Depression

- Only two non-SSRIs with some support for efficacy in adolescents:
  - Nefazodone (Serzone)
    - Increased risk of hepatotoxicity
  - Venlafaxine (Effexor)
    - Post-hoc analysis of two clinical trials:
      - Showed efficacy in adolescent, but not preadolescent, depression
      - As efficacious as fluoxetine in treatment resistant depression
- Bupropion (Wellbutrin):
  - Only open-label studies

Depression

- Treatment-resistant depression
  - Non-response to SSRI: switch to another SSRI and add CBT
  - Non-response with two consecutive trials of SSRIs: consider other classes
    - Ex: Venlafaxine, bupropion
  - If partial response: augment with an antipsychotic, bupropion, or lithium
    - No empirical studies in the youth

ANXIETY
Anxiety
- Several effective approaches, both psychotherapeutic and psychopharmacological, have been documented
  - Studies show additive effects of using combination over either alone
- SSRIs are highly effective
  - Sertraline, fluoxetine, paroxetine, fluvoxamine
  - Efficacious for anxiety experienced while in the feared situation
    Not as good for anticipatory anxiety

OBSESSIVE COMPULSIVE DISORDER

Relative abundance of RCT demonstrating efficacy with:
- SSRIs: Sertraline, fluoxetine, paroxetine, fluvoxamine
  - Fluvoxamine FDA-approved for ≥ 8 years
  - Fluoxetine FDA-approved for ≥ 7 years
  - Sertraline FDA-approved for ≥ 6 years
- Clomipramine
  - FDA-approved for ≥ 10 years
  - Meta-analysis showed superiority to SSRIs
Clomipramine: Adverse Events
- Class: Tricyclic antidepressant
- Adverse Events:
  - Anticholinergic effects
  - CND depression
  - Hematologic effects
  - Orthostatic hypotension
  - Seizures
  - Sexual dysfunction
  - Weight gain
  - Conduction abnormalities

Clomipramine: Monitoring
- Weight
- Pulse rate and BP
  - Prior to and during therapy
- EEG and cardiac status
- LFTs
- CBC with diff
  - In patients who develop fever and sore throat during treatment

Obsessive Compulsive Disorder
- Combination Treatment
  - Studies show superiority of CBT with medication than to medication or CBT alone
  - While medications alone help, CBT is first-line
- Augmentation strategies
  - In adults: SGA, clonazepam, morphine
  - No controlled studies to guide clinicians for child and adolescent treatment-resistance
Nonpharmacological interventions are first-line
- Psychotropics for more severe cases
- Systematic reviews have demonstrated some evidence for use of antipsychotics
- Disagreement in the field exists
  - NICE guidelines do not recommend antipsychotics for core treatment of ASD
  - AACAP guidelines recommend the use of pharmacotherapy when there is a specific target symptom or comorbid condition
- Pharmacotherapy used to allow child to better engage in treatment plans

**ASD: Antipsychotics**
- Management of maladaptive behaviors
- Haloperidol (Haldol)
  - Not FDA approved, but most commonly studied prior the SGA
- Risperidone (Risperdal)
  - FDA-approved for treatment of irritability associated with ASD in 5-15 years
- Aripiprazole (Abilify)
  - FDA-approved for treatment of irritability associated with ASD in 6-17 years
ASD: Antipsychotics

- Other SGA researched in ASD:
  - Olanzapine (Zyprexa)
    - Placebo-controlled, double blind study
    - Positive efficacy for aggression and irritability
  - Agents with modest efficacy in reducing irritability
    - Clozapine (Clozaril)
    - Ziprasidone (Geodon)
    - Quetiapine (Seroquel)

ASD: Antidepressants

- SSRIs studied and used in clinical practice for the repetitive behaviors in ASD
  - Overall efficacy appears inconsistent
    - A systematic review in 2010 showed no data supporting their use in ASD and strong data recording incidence of ADE
  - Antidepressants evaluated:
    - Clomipramine
    - Fluoxetine, sertraline, escitalopram, fluvoxamine

ASD: Psychostimulants

- Psychostimulants for the treatment of ADHD-like symptoms have been used with mixed results
- Amphetamines have limited efficacy data, with no controlled studies since 1970s
  - Results indicate minimal benefit and potential ADE, including worsening of ASD symptoms
- Clonidine and guanfacine: moderate efficacy in reducing stereotypy, hyperactivity, and irritability
Oppositional and Conduct Disorders

- Differing views as to the usefulness of medications
- Prescribing medications is increasing
  - Modest evidence for effectiveness
  - Antipsychotics: risperidone, aripiprazole
    - Clinical experience suggests they can reduce aggression in some cases
  - Mood stabilizers: lithium, carbamezapine
  - Buspirone, clonidine
- Best studied pharmacological interventions in youth with ODD/CD and ADHD: psychostimulants
**Tic Disorders**

- Decision on use of medications depends on clinical presentation and level of symptoms
  - Best to withhold medication use until tic become a significant source of impairment
  - Many cases can be managed without medications
  - Treat co-morbid conditions first
- Goal of pharmacotherapy: use as little medication as possible to render tics more tolerable

**Tic Disorders**

- Typical antipsychotics remain most predictably effective tic-suppressing agents
  - Haloperidol, pimozide, fluphenazine
    - Haloperidole FDA-approved for ≥3 years
    - Pimozide FDA-approved for ≥ 2 years
- To avoid EPS, atypicals have been used to treat tic symptoms
  - Risperidone, olanzapine, ziprasidone, aripiprazole
    - Only aripiprazole FDA-approved for 6-18 years
- Botulinum toxin injections

**Summary**

- Greater barriers to the effective use of psychotropic medications exist in pediatric population
- Psychotropics are not always a last resort treatment
- Use of specific psychotropic agents should be guided by the best available evidence
- Monitoring patients for improvement and ADE should be part of the treatment plan
True or False?

- One barrier to the effective use of psychotropic medications in pediatrics may be inadequate adult supervision.
- Psychotropics are a last resort treatment, only to be used after all other methods have failed.
- The second generation antipsychotics are the standard for treating the first episode of psychosis in pediatric patients with risperidone being the most widely used atypical.

References


References